AMERICAN HEART JOURNAL

February, 1959
Volume 57, No. 2

Editorial

Measurement of Cardiac Efficiency

Robert A. Bruce, M.D., Seattle, Wash.

Efficiency of energy transformation is measured by the amount of work produced for the amount of energy liberated; the remainder is dissipated as heat. When this analysis is applied to the heart, efficiency is the ratio of the product of stroke work and heart rate to the metabolic rate of the heart muscle.

For each heart beat, external stroke work is the sum of work performed by the left and right ventricles in ejecting a volume of blood against the end-diastolic pressure of the aorta and pulmonary artery, and the kinetic energy represented by the mean velocity of the bolus of blood passing the aortic and pulmonic valves. Whereas stroke work should be the integration of internal pressure and volume curves[1] for each of the ventricles, it is conventionally derived from the product of average stroke volume, mean pressure in the proximal arterial tree, specific gravities of blood and of mercury.

Since pulmonary arterial pressure is normally about one sixth that of systemic arterial pressure, the largest part of total cardiac work is performed by the left ventricle. Velocity of blood flow varies directly with stroke volume, and inversely with duration of systolic ejection and cross-sectional area. It is high enough in both the pulmonary artery and aorta in normal resting human subjects to produce turbulent flow. About 1 per cent of the total energy is delivered as kinetic energy.[2] If the velocity is further accelerated by high cardiac output, or by valvular stenosis, the proportion of total energy delivered as kinetic energy may be increased appreciably.

The stroke work per unit of pressure of a dilated ventricle is increased insofar as greater force is necessary to contract against the augmented tension in the wall (where according to Laplace's law tension is the product of pressure and radius), but this work per unit of volume is diminished because a smaller contraction is needed to eject the same volume of blood.[3] Furthermore, the volume

Received for publication Oct. 6, 1958.

ejected from a dilated ventricle is often diminished. In other pathologic situations in which there is valvular regurgitation or intracardiac shunting, the work per stroke of ejecting blood into another chamber should be accounted for in considering total work, even though these increments do not necessarily contribute to "useful" work.

The rate of energy liberated by the myocardium is the product of its oxygen consumption and the work equivalent of oxygen for the ambient respiratory quotient. If the latter is not measured, a value of about 2 kilogram-meters per milliliter of oxygen may be assumed. If all the venous blood from the myocardium drained into the coronary sinus, it would be possible to derive the oxygen consumption of the entire heart from the product of coronary sinus blood flow per minute and the mean arteriovenous oxygen difference. Since the cardinal and thebesian veins drain much of the right heart separately, coronary sinus blood represents venous blood predominantly from the left heart, and not the mixed blood from all venous tributaries. However, the boundaries of these tributaries are not sharply defined. Nevertheless, myocardial oxygen consumption of the "left ventricle" has usually been estimated from sampling venous blood from the coronary sinus, except in more elaborate experimental preparations cited below.

Cardiac efficiency has been calculated variously by different investigators from either the total oxygen consumption or the "net" amount consumed for production of useful work. In the latter instance, the "basal" oxygen consumption for the nonworking (and usually nonbeating) heart under experimental conditions is subtracted from the total value during useful work. Although this formulation reduces the denominator, and efficiency is thereby higher, there is no valid justification for this manipulation of the data.

In 1915, Evans and Matsuoka[4] reported that the efficiency of the canine heart lung preparation approximated 5 per cent at rest. Whereas it increased to nearly 20 per cent with optimal loads of arterial pressure and cardiac output, further increments in pressure or dilation of the heart reduced efficiency. Myocardial oxygen consumption increased more with increased pressure than it did with increased cardiac output. Heart rate in this preparation was more rapid than in situ, and this reduced efficiency. Since the observed efficiency was low, the heart in this preparation was liberating energy in excess of its immediate requirements, yet was able to respond to greater work loads without marked increases in metabolism. "If it were unable to do this, failure would be inevitable."[4] Heart failure due to a decrease in metabolism and a slowing of the rate was also observed.

By utilizing the nitrous-oxide technique to measure coronary blood flow, and the cardiac catheter to withdraw venous blood from the coronary sinus, Bing and associates[5] reported measurements of cardiac efficiency in human subjects in 1949. The average efficiency was 23 per cent in 3 out of 4 normal subjects. It ranged from 13 to 17 per cent in 6 patients with congestive heart failure, due to considerable reduction in useful work and slight increases in oxygen consumption. Although total oxygen consumption was increased by hyper-

trophy, efficiency was not evaluated. By applying the same techniques in the intact, unanesthetized dog, Spencer and colleagues,[6] in 1950, found that the myocardium of the left ventricle received 2.4 per cent of the cardiac output, consumed 5.7 per cent of the total oxygen consumption, and had efficiencies ranging from 20 to 38 per cent. In subsequent clinical studies, except in the presence of myocardial failure, efficiency increased 25 per cent in cardiac patients during exercise sufficient to raise cardiac output about 4 liters, arterial pressure about 30 mm. Hg, and myocardial oxygen consumption 48 per cent.[7] All of these *in vivo* observations were based upon several assumptions. Data for work produced and energy consumed were considered related to the same portion of the heart (left ventricle). Right ventricular work, which could be substantial in the presence of pulmonary hypertension, was not considered. A constant respiratory quotient was assumed to derive work equivalents. Finally, the weight of the left ventricle was estimated from normal values and thereby precluded any correction for hypertrophy.[5]

With the advent of extracorporeal circulation for open heart surgery, further studies indicated that myocardial oxygen consumption during ventricular fibrillation remained the same,[8] diminished,[9,10] or increased.[11,12] When there was adequate coronary perfusion, there was no significant change in vigorous fibrillatory movements, myocardial concentrations of glycogen or adenosinetriphosphate, or consumption of oxygen.[11] Subsequent observations of myocardial oxygen consumption in the experimental absence of cardiac work (by rapid exsanguination with suction, by vagally induced cardiac arrest, or by potassium arrest) indicated values ranging from 16 to 40 per cent of prior levels obtained during work.[13] Consequently, it was suggested that efficiency be defined as the ratio of work produced to the "net" energy liberated for work. The basal oxygen consumption of the nonworking heart should be disregarded, "since as in any other muscle, its efficiency is estimated by dividing its external work by the difference between its oxygen consumption during the beating state, and during relaxation."[14] Earlier investigators considered a similar proposal by Rohde and Ogawa, in 1912, to discount the energy cost of the nonworking muscle as neither "legitimate" nor "helpful."[4]

Utilizing an ingenious experimental design, Alella and colleagues,[15] in 1955, reported on experimental observations in open chest dogs in which both systemic arterial circulation and regulatory mechanisms were intact. Coronary artery flow increased with aortic pressure, but only in response to the increased metabolic activity of the myocardium. Further studies at three rates of cardiac output and three levels of arterial pressure clearly demonstrated that myocardial oxygen consumption increased more with pressure work than with volume work.[16] Cardiac efficiency was low under all of these experimental conditions and showed no consistent relationship to the work performed. Actually, myocardial oxygen consumption was more closely related to oxygen availability (arterial oxygen content times blood flow) than it was to the amount of external work performed. Acceleration of heart rate also increased myocardial oxygen consumption. Accordingly, the biologic significance of "efficiency" was questioned as a suitable measure of cardiac performance, for "low values of 'efficiency' do not necessarily indicate an insufficient heart nor one beating ineffectively."

Recently, Sarnoff and colleagues[17] demonstrated with a nonfailing, metabolically supported, isolated heart preparation that the average maximum aortic pressure, cardiac output, and ventricular work observed under these conditions were two- to fourfold greater than reported in previously available preparations. In other words, previous techniques of isolating the heart yielded observations where some degree of failure had developed, presumably because of the lack of metabolic support. In contrast, the isolated supported heart (ISH) did not exhibit depressed ventricular function curves, nor the descending limb of Starling's curve. Such a preparation was stable for hours, easily monitored continuously, and rate, output, and pressure were readily controlled independently. Under these circumstances, a myocardial oxygen debt could not be detected. Myocardial oxygen consumption increased with increased left ventricular work resulting from elevations in aortic pressure, but showed only slight increases when cardiac output was augmented with the same mean aortic pressure. At any given work load, accelerating heart rate increased myocardial oxygen consumption and thereby lowered efficiency. When flow was raised, but pressure lowered and heart rate held constant, efficiency was raised from approximately 5 to 20 per cent. External work increased 128 per cent, yet myocardial oxygen consumption declined 20 per cent. Accordingly, it became clear that myocardial oxygen consumption bore little relation to the external work of the heart, but rather was quite closely related to the duration and magnitude of tension developed during systole. The latter was measured in terms of a Tension-Time Index (TTI), or product of mean systolic ventricular pressure and the duration of systole, expressed in mm. Hg seconds per heart beat.[18] These investigators considered the conventional usage of efficiency of the heart with respect to ratio of external work developed to myocardial oxygen consumption meaningful only in terms of the relationship of the heart to the total organism. It was not informative about the energetics of the contracting myocardium. Hence, they proposed the concept of "internal efficiency" to describe the relationship between total tension developed during systole and the oxygen requirement for myocardial contraction. Since the TTI was only an index of total tension in myocardial fibers, without regard to the radius of the chamber, the actual fiber tension developed would be greater in a dilated heart than in a normal heart.

Experimentally, absolute measurements of efficiency of the heart are difficult and somewhat arbitrary as to circumstances and methods. Meanwhile, data are accumulating about direction and magnitude of changes in "stroke work," defined as the product of left ventricular pressure and dimensions (rather than volume) of the heart by Rushmer's techniques.[19] Preliminary observations of left ventricular work in man based upon biplane cineangiofluorographic technique and aortic pressure have been reported.[20] Whereas the stroke volume and work in a normal subject were 84 c.c. and 10,521 Gm. cm. (0.5 per cent kinetic and 99.5 per cent potential), the values in a patient with a markedly dilated left ventricle were 89 c.c. and 29,454 Gm. cm. (1.3 per cent kinetic and 98.7 per cent potential, respectively). Although such measurements of work are now becoming feasible, measurements of efficiency are still handicapped by the problems in measuring myocardial oxygen consumption with comparable precision.

REFERENCES

1. Burch, G. E., Ray, C. T., and Cronvich, J. A.: Circulation **5**:504, 1952.
2. Prec, O., Katz, L. N., Sennett, L., Rosenman, R. H., Fishman, A. P., and Hwang, W.: Am. J. Physiol. **159**:483, 1949.
3. Rushmer, R. F.: Cardiac Diagnosis—A Physiologic Approach, Chapter 7, Ventricular Distensibility and Contractility, Philadelphia, 1955, W. B. Saunders Company.
4. Evans, C. L., and Matsuoka, Y.: J. Physiol. **49**:378, 1915.
5. Bing, R. J., Hammond, M. M., Handelsman, J. C., Powers, S. R., Spencer, F. C., Echerhoff, T. E., Goodale, W. T., Hafkenschiel, J. H., and Ketry, S. S.: Am. Heart J. **38**:1, 1949.
6. Spencer, F. C., Merrill, D. L., Powers, S. R., Bing, R. J.: Am. J. Physiol. **160**:149, 1950.
7. Lombardo, T. A., Rose, L., Taeschler, M., Tuluy, S., and Bing, R. J.: Circulation **7**:71, 1953.
8. Senning, A.: Acta chir. scandinav. Suppl. **171**:1, 1952.
9. Pederson, A., Siegel, A., and Bing, R. J.: Am. Heart J. **52**:695, 1956.
10. Beuren, A., Sparks, C., and Bing, R. J.: Am. J. Cardiol. **1**:103, 1958.
11. Paul, N. H., Thielen, E. O., Gregg, D. E., Marsch, J. B., and Carter, G. G.: Circulation Res. **2**:573, 1954.
12. Jardetzky, O., Greene, E. A., and Lorber, V.: Circulation Res. **4**:2, 1956.
13. McKeever, W. F., Carney, C. P., and Gregg, D. E.: J. Lab. & Clin. Med. **48**:923, 1956.
14. Gregg, D. E., and Sabiston, D. C.: Circulation **13**:916, 1956.
15. Alella, A., Williams, F. L., Bolene-Williams, C., and Katz, L. N.: Am. J. Physiol. **183**:570, 1955.
16. Alella, A., Williams, F. L., Bolene-Williams, C., and Katz, L. N.: Am. J. Physiol. **185**:487, 1956.
17. Sarnoff, S. J., Case, R. B., Welch, G. H., Jr., Braunwald, E., and Stainsby, W. N.: Am. J. Physiol. **192**:141, 1958.
18. Sarnoff, S. J., Braunwald, E., Welch, G. H., Case, R. B., Stainsby, W. N., and Macruz, R. Am. J. Physiol. **192**:148, 1958.
19. Rushmer, R. F.: Cardiac Diagnosis—A Physiologic Approach, Chapter 6, The Regulation of Cardiac Output, Philadelphia, 1955, W. B. Saunders Company.
20. Baker, O., and Chapman, C. B.: Clin. Res. Proc. **6**:212, 1958.

Paroxysmal Ventricular Tachycardia: A Clinical and Electrocardiographic Study

George R. Herrmann, M.D., Hi Myung Park, M.D., and Milton R. Hejtmancik, M.D., Galveston, Tex.

Paroxysmal ventricular tachycardia is, fortunately, a rather uncommon disorder of the cardiac mechanism, but it may produce such serious complications that, in general, it must be promptly recognized and halted in order to forestall dissolution. Paroxysmal ventricular tachycardia (PVT) occasionally occurs in healthy individuals who show no reliable signs of heart disease, and who apparently have other wise normal hearts by our clinical standards. Paroxysms may be precipitated by cardiac catheterization and may also be very serious developments during cardiac surgery. The majority of paroxysms of ventricular tachycardia, however, too often develop in patients with significant heart disease and extensive myocardial damage, and add greatly to the seriousness of the situation. The paroxysm may precipitate or aggravate myocardial failure and impose an additional load upon the already overloaded heart. In some instances, PVT seems to be a prefibrillary state that progresses to ventricular fibrillation, which is practically incompatible with life.[1-4]

Symptoms.—The symptoms may be very disturbing, rapid palpitation, augmented precordial activity, severe dyspnea and acute pain of relative coronary insufficiency or of actual coronary thrombosis, extreme weakness or prostration, or general circulatory collapse or blackout with, at times, cerebral episodes. Any of these manifestations may present an emergency situation requiring immediate diagnosis and prompt treatment.

Signs.—The signs are those of rapid heart action which may be barely recognizable as irregular, and which does not respond at all to carotid sinus pressure or vagus nerve stimulation; with occasionally a transient rise, but usually a fall, in blood pressure and one or more of the reliable signs of heart disease. Syncope, collapse, or acute left heart failure with pulmonary edema may be presenting manifestations.

From The Cardiovascular Service and Heart Station of the University of Texas Medical Branch Hospital, Galveston, Tex.

Supported in part by grants in aid from the H. H. Weinert Fund for Cardiovascular Research.

Presented at the 31st Annual Meeting of the American Heart Association, Oct. 20, 1958, in San Francisco, Calif.

Received for publication Oct. 24, 1958.

Our experiences with the patients presenting PVT during the decade 1937 to 1947 were reported in 1948.[5] The added experiences of the past decade seem to us to warrant another summarization, inasmuch as new antiarrhythmic agents—procaine amide, chloroquine, and tranquilizers such as Atarax—have been introduced and occasionally found effective. The routine electrocardiographic studies in this series have been much more extensive and have included in the 12 leads the so-called unipolar extremity and precordial leads in all cases. We believe that electrocardiographic monitoring must always be carried out during the intravenous injection of these active therapeutic agents. The effects of the traditional quinidine, intravenously, intramuscularly, or orally, and the newer agents such as procaine amide, are recorded. It was hoped, and realized, that the old facts would be substantiated and that important new points of interest would be uncovered and emphasized and the most effective therapeutic procedures would be established.

THE DIAGNOSTIC CRITERIA

In any study of medical conditions, especially studies in which methods of precision are used, it is desirable and necessary to delineate the criteria for diagnosis. Fortunately, the electrocardiographic criteria for PVT as first set down by Herrmann and Robinson[1] have stood the test of time, have been accepted generally, and have been restated clearly in the more recent reports on the subject from this and other laboratories. The criteria were reaffirmed by us previously and are restated herewith. As our experience has increased, we have encountered more instances in which there was great difficulty in establishing the correct electrocardiographic diagnosis which is so necessary for successful treatment. There have been additions to our knowledge of the subject and for the differentiation of supraventricular tachycardia with bundle branch block and the pseudoventricular tachycardias of A-V accelerated conduction which we have recently emphasized.[8]

The clinical picture, attacks of rapid palpitation with extreme weakness, dyspnea, or pain developing especially in middle-aged patients or in patients with known heart disease, should alert the physician. Tachycardia in severe heart disease of rheumatic, hyperthyroid, hypertensive, or coronary atheromatous origin should immediately suggest the possibility of the inception of the generally more serious and complicating cardiac mechanism disorder, paroxysmal atrial, nodal, or ventricular tachycardia. Our study of the supraventricular type was published recently.[8a]

On physical examination, ventricular tachycardia, in minute-to-minute counts of the pulse, is suggested by (1) slight irregularity, with rates differing by 5 to 7 beats from minute to minute, (2) occasional giant waves in the jugular pulses, (3) changing intensity and quality of the first heart sound in the presence of tumultuous precordial sounds of low frequency,[9] staccato in type, (4) failure of the heart rate to slow on carotid sinus or oculocardiac, indirect vagal, stimulation. These are strongly suggestive of the diagnosis. However, not one of these clinical signs alone, nor all of them together, may be considered

pathognomonic of PVT. Irregularity of the ventricular rhythm may be produced by disturbances in the A-V conduction of impulses formed regularly by a supraventricular ectopic pacemaker.[6]

The diagnosis of PVT can be made with certainty only after careful analysis of the electrocardiogram. The criteria which we previously established[1] and reaffirmed[5] consists of three important features or findings: (1) the presence of runs of abnormal ventricular complexes varying slightly in contour due to occasionally superimposed P waves; (2) the establishment of atrial complexes, P waves, occurring independently and usually at a slower rate, rarely retrogradely[11]; (3) the finding of isolated ventricular complexes before and after a paroxysm that have the same form as the ventricular complexes recorded during the paroxysm. The isolated premature ventricular contractions must bear the same relationship to the normal ventricular complexes as do the onset and offset complexes of the tachycardia.[1-9]

THE CLINICAL MATERIAL OF THIS STUDY

A series of 84 episodes of PVT in 60 patients has been analyzed, with the diagnosis in each being based on the aforementioned ECG criteria. This study covers all cases of established PVT observed in the University of Texas Hospitals between October, 1947 and October, 1957.

As in our previous study,[5] we arbitrarily divided PVT into two groups, the intermittent type and the persistent type.[10] Included in the intermittent type are those patients in whom runs of four or more ectopic ventricular contractions of less than 30 seconds' duration have been recorded electrocardiographically, and in the persistent type are those patients in whom a continuous run of longer duration has been recorded. Some of the patients with the persistent type and many of the patients with the intermittent type have had one or more episodes of the intermittent type, but these instances were not counted as separate episodes unless they were recorded on different days. In this study, 38 persistent episodes and 46 intermittent episodes of PVT fulfilling our criteria were observed.

The distribution of PVT cases by age, in decades, is shown in Fig. 1, *A* and is in general agreement with the data of comparable series,[16,17] as well as with our earlier experiences. The youngest patient was 9 months old, and the oldest was 97 years old. About 80 per cent of the patients were between the fifth and seventh decades. There were 34 males and 25 females. Thirty-four patients were white and 25 were Negroes. Twenty-eight patients had exhibited the persistent type of PVT and 31, the intermittent type. There were no significant differences between the persistent type and intermittent type in regard to age, sex, and race.

ETIOLOGICAL DATA

The underlying types of heart disease in our patients with PVT are listed in Table I. Atherosclerotic coronary ischemic heart disease with or without hypertensive cardiovascular disease and rheumatic heart disease were present in 71 and 12 per cent of the cases, respectively. Many of the patients had associated acute myocardial infarction, and this was particularly true in those with the persistent type of PVT. Details of arteriosclerotic heart disease cases are given in Table II. There were no significant differences in the type of heart disease in those patients with the persistent type and in those with intermittent type of ventricular tachycardia.

PVT in Patients With No Heart Disease.—It has been amply shown by individual case reports as well as in the studies of large series[13,4] that PVT may occur in the normal heart. Six patients, or 10 per cent, in our series had no ap-

parent reliable sign of organic heart disease; the precipitating factors in these cases are given in Table III. One patient, a 15-year-old boy, had two episodes of PVT of the persistent type during a 2-month period, and one of the episodes lasted about 3 days. Attacks in this case were considered to be precipitated by emotional strain. Another case, a 21-year-old man, had had multiple episodes of tachycardia since 1946, and six of those episodes were proved by ECG to be PVT. Episodes in this case were definitely associated with anxiety and emotional excitement. Similar recurrent types of PVT of years' duration in persons with young normal hearts have been reported by Froment and associates.[10] Hypokalemia due to severe diarrhea, a beer binge, a chromophobectomy, and lower nephron nephrosis were isolated causes of PVT. One of us observed PVT in two young women who had perfectly normal hearts; both women have long outlived their husbands.[13]

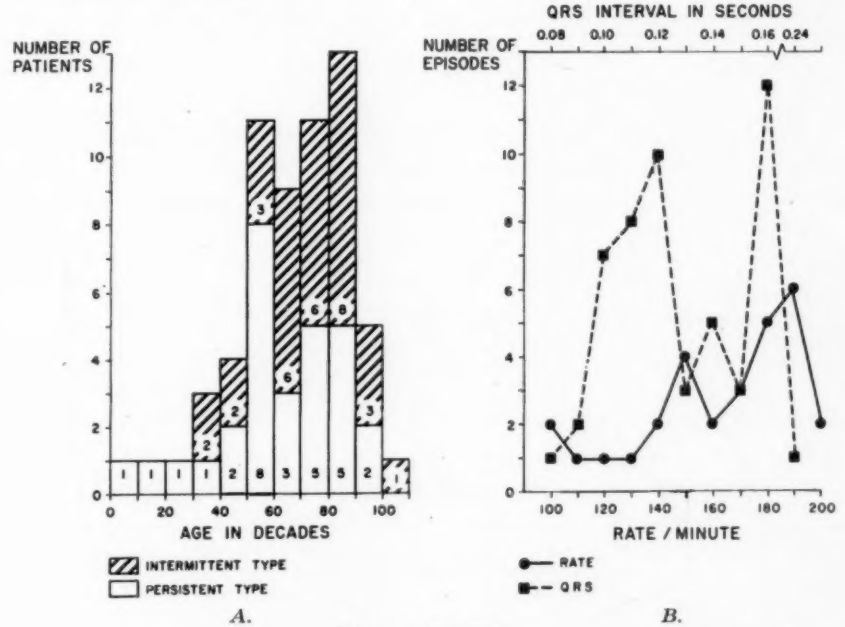


Fig. 1.—See text.

PVT Due to Digitalis Intoxication.—Digitalis as a precipitating factor of PVT is well known.[12] The role that digitalis played in our series is shown in Table IV, which reveals that 10 per cent of the patients had definite evidence of digitalis intoxication at the time of the PVT; in another 17 per cent of the cases digitalis overdosage could not be definitely ruled out. Digitalis in moderate dosage was prescribed in another 27 per cent of the cases, while 46 per cent of the patients had received no digitalis. One patient, a 9-month-old infant with congenital heart disease, had two attacks of persistent PVT, both of them associated with digitalis intoxication. Digitoxins were the preparations most commonly incriminated.

Clinical Features.—The symptoms and signs in patients with PVT may be arranged in three categories: (1) those of the underlying heart disease, such as myocardial infarction or congestive heart failure; (2) those due to precipitating

factors, such as digitalis overdosage; and (3) those due to the tachycardia itself. However, it is difficult at times to ascertain to what degree the tachycardia itself is responsible for the symptoms and signs, because of the similarity of clinical manifestations in each of the three categories (Table XIII).

TABLE I. ETIOLOGY OF VENTRICULAR TACHYCARDIA

TYPE OF HEART DISEASE	PERSISTENT TYPE	INTERMITTENT TYPE	TOTAL
Arteriosclerotic heart disease	20	22	42 (71%)
Rheumatic heart disease	4	3	7 (12%)
Heart disease due to thyrotoxicosis	0	2	2 (3%)
Congenital heart disease	2	0	2 (3%)
No organic heart disease	2	4	6 (10%)
Total	28	31	59

TABLE II. DETAILS OF ARTERIOSCLEROTIC HEART DISEASE

	PERSISTENT TYPE	INTERMITTENT TYPE	TOTAL
With acute myocardial infarction	9	4	13
Without acute myocardial infarction or hypertension	6	11	17
With hypertension	5	7	12
Total	20	22	42

TABLE III. DETAILS OF PATIENTS WITH PVT AND NORMAL HEARTS

SEX	AGE	PRECIPITATING FACTORS	TYPE OF PVT
M	15	Emotional excitement	Persistent
M	21	Emotional excitement	Intermittent
F	56	Severe diarrhea of unknown origin	Intermittent
M	49	Surgical removal of chromophobe adenoma of pituitary gland under general anesthesia with ether and Pentothal	Persistent
M	23	Consumption of 15 cans of beer	Intermittent
M	39	Hypokalemia in a patient with nephrosis	Intermittent

TABLE IV. DIGITALIS STATUS OF PATIENTS AND TYPE OF PVT

	PERSISTENT	INTERMITTENT	TOTAL
Toxicity	4	2	6 (10%)
Probable toxicity	4	6	10 (17%)
Moderate dose	8	8	16 (27%)
No digitalis	12	15	27 (46%)

Many of the patients with the intermittent type, and, in rare instances, a patient with the persistent type, may be unaware of tachycardia. Congestive heart failure, mild to severe, was present in 63 per cent of the patients with the persistent type and in 57 per cent of the patients with the intermittent type. Dyspnea and weakness, caused primarily by underlying disease but aggravated by tachycardia, were the most common symptoms regardless of the type of PVT. Cardiac chest pain and strong palpitation were also rather common complaints.

TABLE V. DURATION OF PVT IN PERSISTENT TYPE (38 EPISODES)

DURATION	NUMBER OF EPISODES
Less than 1 hour	15
1 to 12 hours	10
12 to 24 hours	8
24 to 36 hours	3
3 days	1
7 days and 6 hours	1

TABLE VI. RHYTHM BEFORE PVT

RHYTHM	PERSISTENT TYPE	INTERMITTENT TYPE	TOTAL
Sinus rhythm	13 (1 with LBBB)	13 (1 with LBBB, 2 with RBBB)	26
Atrial fibrillation	5 (1 with LBBB)	7 (1 with LBBB)	12
Paroxysmal atrial tachycardia	1	0	1
Supraventricular tachycardia	1	0	1

TABLE VII. RHYTHM AFTER PVT

RHYTHM	PERSISTENT TYPE	INTERMITTENT TYPE	TOTAL
Sinus rhythm	14	15	29
Atrial fibrillation	5	7	12
Atrial flutter	0	1	1

Very few cases had cerebral manifestations such as dizziness or syncope (Table XIII). In about 30 per cent of the cases with the persistent type of PVT the blood pressure had to be maintained with a sympathomimetic vasopressor, most often Levophed. The rate of the tachycardia in the persistent type varied from 104 to 231 per minute (Fig. 1,*B*). In about 70 per cent of the episodes it ranged between 130 and 200 per minute. The duration of the QRS intervals are shown in Fig. 1. The length of the attacks of PVT varied from a few seconds to days, the longest being 7 days and 6 hours. The duration of the episodes of the persistent type of PVT in 38 instances is given in Table V. Three cases of bidirectional paroxysmal ventricular tachycardia will be reported separately.

In 40 out of 57 patients, previous and subsequent electrocardiograms taken within a year and usually within a few months prior to the paroxysm were available. In 42 patients, electrocardiograms taken within a few months, and most often within a few days or hours, after the cessation of tachycardia were available. The rhythm before and after PVT is given in Tables VI and VII. These show that in about 40 per cent of the cases, atrial fibrillation was present either before, with, or after the development of PVT.

The effects of therapeutic agents in our patients are shown in Table VIII. Procaine amide was most often used (0.25 to 1.0 Gm., intravenously) and was successful in 10 of 12 cases, while quinidine alone (0.4 Gm.p.o. hourly for 6 to 8 doses) was successful in all of the 5 cases in which it was used. Morphine alone (0.015 to 0.045 mg., intravenously) stopped 2 of the 3 episodes, and combinations were similar and quite successful. This is in keeping with our previous experience.[18-20]

TABLE VIII. EFFECTS OF THERAPEUTIC AGENTS

TYPE OF TREATMENT	NUMBER OF TRIALS	NUMBER OF CASES CONVERTED
Quinidine alone	5	5
Quinidine plus Morphine	3	2
Quinidine plus Pronestyl	4	3
Pronestyl alone	12	10
Morphine	3	2
Total	27	22

TABLE IX. PROGNOSIS

	PERSISTENT TYPE		INTERMITTENT TYPE	
	TOTAL CASES	NUMBER OF DEATHS	TOTAL CASES	NUMBER OF DEATHS
ASHD with myocardial infarction	9	7	4	3
ASHD without myocardial infarction	11	7	18	8
Rheumatic heart disease	4	2	3	1
Heart disease due to thyrotoxicosis			2	0
Congenital heart disease	2	1	0	0
No organic heart disease	2	1	4	1
Total	28	18 (64%)	31	13 (42%)

Prognosis.—In our first and second series we emphasized the seriousness of the prognosis in most of our hospitalized patients with PVT. In Strauss' review,[14] 40 out of 50 patients having PVT with organic heart disease were dead within 3 hours to 6 months after the onset of the tachycardia, with an average survival period of 24 days. Cooke and White[15] reported that in a group of 21

patients with PVT in coronary heart disease 17 died within a few hours to 18 months. In the series of Williams and Ellis,[16] 20 out of 36 patients died within a month. However, it is well known that the prognosis in those with no heart disease is excellent—our two special cases cited are living after 20 and 40 years—although even in this group sudden death may occur.[17]

The relationship between the type of underlying heart disease, the type of PVT, and the number of deaths, 64 per cent of those with persistent and 42 per cent of those with intermittent PVT, is shown in Table IX. The breakdown with respect to prognosis from follow-up data is listed in Table X. One of 2 patients with persistent PVT and one of the 4 patients with intermittent PVT and no apparent heart disease died; one patient could not be followed up. As shown in Table XI, of 10 patients with nonfatal persistent PVT, 5 were alive after 19 months to 9 years from the onset of PVT; 3 were alive after 1 to 4 years; 1 patient could not be followed up after 3 months; and 1 patient was not followed after discharge. Of 18 patients with nonfatal intermittent PVT, 3 were alive after 27 months to 11 years from the onset of PVT; 5 were alive after 2 months to 7 years from the onset of PVT; and 10 were not followed after discharge. The remaining 2 patients with no apparent heart disease had died. In the case in which PVT followed craniotomy, and in the other case in which PVT developed after 3 weeks of severe diarrhea of unknown origin, death occurred shortly after the onset of PVT. The cause of death in these cases was considered to be noncardiac, but both patients may have died from hypopotassemia.

TABLE X. FOLLOW-UP

Persistent Type (Total 28 Cases)		Intermittent Type (Total 31 Cases)	
Fatal cases (Total 18 Cases)		Fatal cases (Total 13 Cases)	
Within 1 week	13	Within 1 week	6
Within 2 months	4	Within 1 month	5
After 33 months	1	Within 10 months	2
Congenital heart disease, type undetermined, associated with digitalis intoxication			

TABLE XI

Persistent PVT, Nonfatal Cases (Total 10 Cases)
- 5 alive after 19 months to 9 years from onset of PVT
- 3 alive after 1 to 4 years
- 1 patient followed for 3 months until lost, and 1 patient not followed after discharge

Intermittent PVT, Nonfatal Cases (Total 18 Cases)
- 3 alive after 27 months to 11 years from onset of PVT
- 5 alive after 2 months to 7 years from onset of PVT
- 10 not followed after discharge

Table X shows that out of the 31 patients with PVT of the intermittent type, 13 or 42 per cent died within 10 months after the onset of PVT, while of 28 patients with the persistent type, 17 or 61 per cent died within 2 months and 1 lived for 33 months. It is also noted that PVT is a very serious complication

when it occurs in association with acute myocardial infarction. In 13 cases there were 10 deaths, a mortality rate of 77 per cent, in contrast to 15 deaths, or 50 per cent, in 29 cases with ASHD and PVT but without acute infarction. Prognosis in the intermittent type is somewhat better than in the persistent type, the mortality rates being 42 and 64 per cent, respectively. There was no close correlation between rate per minute of the PVT and the mortality rate. Five patients with persistent PVT died of PVT itself, although this was not proved by ECG at exitus.

TABLE XII. DIGITALIS AND PROGNOSIS

	TOTAL CASES	NUMBER OF DEATHS
Toxicity	5	3
Probable Toxicity	11	8
Moderate Dose	16	7
None	27	13

TABLE XIII. CLINICAL FEATURES IN PATIENTS WITHOUT MYOCARDIAL INFARCTION

	INTERMITTENT TYPE	PERSISTENT TYPE	TOTAL
Congestive heart failure	16	9	25
Weakness	4	6	10
Chest pain	5	3	8
Palpitation	3	3	6
CNS (fainting, dizziness)	2	2	4
Vomiting	3	2	5
Shock	2	2	4
Dyspnea associated with PVT	—	4	4

The prognosis of PVT may be influenced by many factors, including duration, rate, etiology of tachycardia, response to therapy, precipitating factors, and type and seriousness of the underlying heart disease. Tachycardia of any origin may lead to myocardial failure by imposing an excessive load on the heart, lowering cardiac output, and decreasing coronary perfusion. From this point of view the duration and rate of the PVT and, therefore, the therapeutic response, cannot be ignored in the matter of prognosis. This is exemplified by better prognosis in the intermittent type than in the persistent type in this study, as well as in those of others.[11] On the other hand, the high mortality rate of PVT, especially in patients with acute myocardial infarction, is a source of worry despite the fair therapeutic response (80 per cent converted to normal sinoatrial rhythm) in our series, as well as in others'. The good prognosis in those patients with no organic heart disease is indicative of the importance of the role played by the nature of the underlying heart disease.

It is also likely that patients with serious myocardial damage are prone to develop the long-lasting, persistent type of PVT. It is felt that the prognosis

of PVT is greatly influenced by the duration of PVT but particularly by the seriousness of underlying heart disease.

Table XII shows that of 16 cases with definite and probable digitalis intoxication, 11 died. The clinical features present in 35 intermittent and 31 persistent episodes in patients without myocardial infarction are shown in Table XIII; weakness and chest pain were equally prominent in both intermittent and persistent types, but dyspnea was more common in the persistent type.

SUMMARY OF STUDY OF PVT

Records of 60 patients presenting 84 episodes of PVT fulfilling our criteria were analyzed. The final criteria accepted for the diagnosis of PVT in this study were as follows: (1) Tumultuous tachycardia with variations of 5 to 7 beats in full minute-to-minute counts. (2) Changing intensity and quality of the first heart sound at the apex occurring as the atrial and ventricular contractions were superimposed. (3) Occasional giant jugular venous pulse waves. (4) Failure of the tachycardia to slow on carotid sinus pressure or any indirect vagus stimulation. (5) Usually one or more of the reliable criteria of organic heart disease. (6) Symptoms such as (a) extreme weakness, prostration, (b) tumultuous palpitation, (c) severe dyspnea, cough and, at times, frothy, blood-tinged expectoration. (7) In elderly individuals, cardiac pain, anginal or persistent, blackout, collapse, syncope or cerebral episodes. (8) Runs of four or more sequential abnormal ventricular complexes with changing contours due to superimposed P waves. (9) The presence of independent atrial complexes, P waves with longer P-P intervals of a slower atrial rhythm, and in rare instances retrograde P waves. (10) Isolated ventricular complexes of the same form before and after the paroxysm, and bearing the same time relationship to normal ventricular complexes as do the onset and offset complexes of the paroxysm.

The cases of PVT were divided into two types: intermittent, less than 30 seconds in duration; and persistent, over 30 seconds in duration. The type of PVT was not related to age, sex, or race.

Underlying arteriosclerotic heart disease was diagnosed in 71 per cent, and rheumatic heart disease in 12 per cent of the cases. There was no heart disease in 10 per cent of the cases presenting PVT. Remarks on the 6 patients with normal hearts and PVT are tabulated and the role of anxiety, apprehension, emotional stress, and hypokalemia is emphasized.

Digitalis intoxication was definite in 10 per cent and probable in 17 per cent; moderate dosage was used in 27 per cent, but 42 per cent had had no digitalis.

The rates of tachycardia were from 104 to 231 per minute, and the lengths of the QRS interval were not related to the duration of the attacks, which lasted from a few seconds to seven and a half days. Of the 42 electrocardiograms taken before and after a paroxysm, about 40 per cent showed atrial fibrillation.

The prognosis is very poor in patients with myocardial infarction even after the PVT has been promptly stopped by therapy. In any case, PVT adds to the seriousness of the outlook.

REFERENCES

1. Herrmann, G. R., and Robinson, G. C.: Heart **8**:59, 1921.
2. Marvin, H. M., and White, P. D.: Arch. Int. Med. **29**:403, 1922.
3. Levine, S. A.: AM. HEART J. **3**:177, 1927.
4. Wiggers, C. J.: AM. HEART J. **20**:399, 1940.
5. Herrmann, G. R., and Hejtmancik, M. R.: Ann. Int. Med. **28**:989, 1948.
6. Langendorf, R., Lev, M., and Pick, R.: Acta cardiol. **7**:241, 1952.
7. Dunn, J. J., Sarrell, W., and Franklin, R. B.: AM. HEART J. **47**:462, 1954.
8. Herrmann, G. R., Oates, J. R., Runge, T. M., and Hejtmancik, M. R.: AM. HEART J. **53**:254, 1957.

8a. Hejtmancik, M. R., Herrmann, G. R., and Wright, J. C.: AM. HEART J. **56**:671, 1958.

9. Harvey, W. P., and Corrado, M. A.: New England J. Med. **257**:325, 1957.
10. Froment, R., Gallavardin, L., and Cahen, P.: Brit. Heart J. **15**:172, 1953.
11. Foster, R. F., and Thayer, R. H.: AM. HEART J. **40**:224, 1950.
12. Gilson, J. S., and Schemm, F. R.: Circulation **2**:285, 1950.
13. Wilson, F. N., Wishart, S. W., Macleod, A. G., and Barker, P. S.: AM. HEART J. **8**:155, 1932.
14. Strauss, M. B.: Am. J. M. Sc. **179**:337, 1930.
15. Cooke, W. R., and White, P. D.: Brit. Heart J. **5**:33, 1943.
16. Williams, C., and Ellis, L.: Arch. Int. Med. **71**:137, 1943.
17. Armbrust, C. A., and Levine, S. A.: Circulation **1**:28, 1950.
18. Sabathie, L. G.: AM. HEART J. **33**:819, 1947.
19. Stempien, S., and Katz, K. H.: AM. HEART J. **24**:555, 1942.
20. Kennamer, R., and Prinzmetal, M.: Med. Clin. North America, Sept. 1956, p. 1313.

Pulseless Disease (Takayashu's Syndrome)

S. S. Misra, M.D. (Hons.), F.R.C.P. (London), Satya Prakash, M.D. (Medicine), and Prem Lata Agrawal, M.B., B.S., Lucknow, India

INTRODUCTION

In 1908, Takayashu[1] described a peculiar syndrome characterized by absence of pulsations in the carotid and the radial arteries. This physical finding is met with in aortic arch syndromes like syphilitic aneurysms, rarely in dissecting aneurysms, and also in traumatic injuries of the chest. There still remains a group of patients in whom there is a primary panarteritis of unknown etiology, and this has been variously described as Takayashu's disease or pulseless disease. It is a rare syndrome affecting chiefly young female adults; hence, it has also been called "young female arteritis." Caccamise and Whitman[2] found 58 cases of this disease reported from Japan.

In spite of the great importance attached to the examination of the pulse in clinical medicine, only two cases of this disease have so far been reported from India, one case by Shikhare,[3] and one by Sen-Gupta and Ghosh,[4] showing thereby the rarity of the condition. Shikhare[3] reported a case with bilateral absence of pulse in the upper limbs and in the carotid arteries, and the autopsy showed an aortic aneurysm containing an ante-mortem clot which sent fingerlike projections into the great arteries, causing obstruction. Sen-Gupta and Ghosh[4] reported a case in which the aorta showed innumerable calcific plaques and a grayish-white friable clot completely occluding the mouths of all three branches.

We present three cases of this rare disease, two of which presented an associated nephrotic syndrome due to amyloidosis, a combination not reported so far in the literature.

CASE REPORTS

CASE 1.—C. L., an 18-year-old male Hindu, complained of enlargement of cervical lymph nodes for the last 6 months, general anasarca, giddiness, and general weakness for 3 months before admission. The lymph glands became suppurative and a few of these glands burst. The patient looked older than his age. Radial, brachial, and carotid pulses were absent on both sides. A prolonged thrill and a continuous machinery-like murmur, more marked during systole, was heard on the right side between the clavicle and the sternomastoid. The femoral pulse was faintly palpable, while the popliteal pulse was absent, and no blood pressure was recordable in any limb.

From the Department of Medicine, K. G. Medical College, Lucknow, India.
Received for publication Sept. 11, 1958.

Urine showed albumin ++++, a fair number of pus cells, stray granular and hyaline casts, and culture showed growth of *Staphylococcus albus*. Serum cholesterol was 269 mg. per cent, while serum proteins were 2.9 Gm. per cent, with albumin 1.5 Gm. per cent. The fundus showed blurred margins of the disc, tortuous and dilated veins, and normal arteries. The Wassermann reaction and V.D.R.L. tests were negative. The tuberculin test was negative, and lymph-gland biopsy showed suppurative lymphadenitis (Fig. 1). Radial artery biopsy showed a normal picture. The patient died, and a partial autopsy was done. On histology, the aorta showed thickened and hyalinized intima (Fig. 2). The media showed infiltration with chronic inflammatory cells, chiefly lymphocytes around the vasa vasora (Fig. 3). The adventitia also showed cellular infiltration at places. The heart showed amyloid deposits, focal granulomatous myocarditis, and coronary sclerosis. The kidneys showed amyloidosis (Fig. 4).

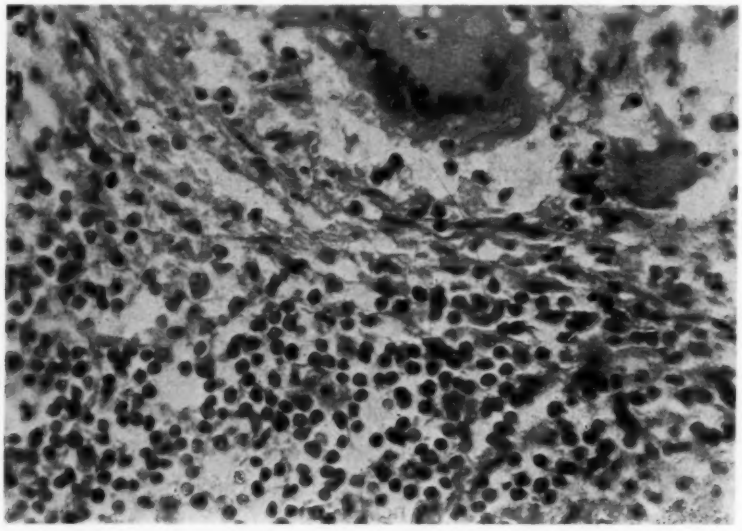


Fig. 1.—Suppurative lymphadenitis. No caseation seen. (Magnification × 360.)

Fig. 2.—Aorta showing thickened and hyalinized intima. (Magnification × 80.)

COMMENT

This patient was a typical case of pulseless disease or Takayashu's syndrome. The aorta showed histologic evidence of panarteritis, of undetermined etiology. Generalized amyloidosis might have been due to the chronic suppurative cervical lymphadenitis, and the nephrotic syndrome was secondary to the renal amyloidosis. Whether or not there was any correlation between amyloidosis and pulseless disease is difficult to say.

Fig. 3.—Aorta. Media showing infiltration with chronic inflammatory cells, chiefly lymphocytes. (Magnification × 160.)

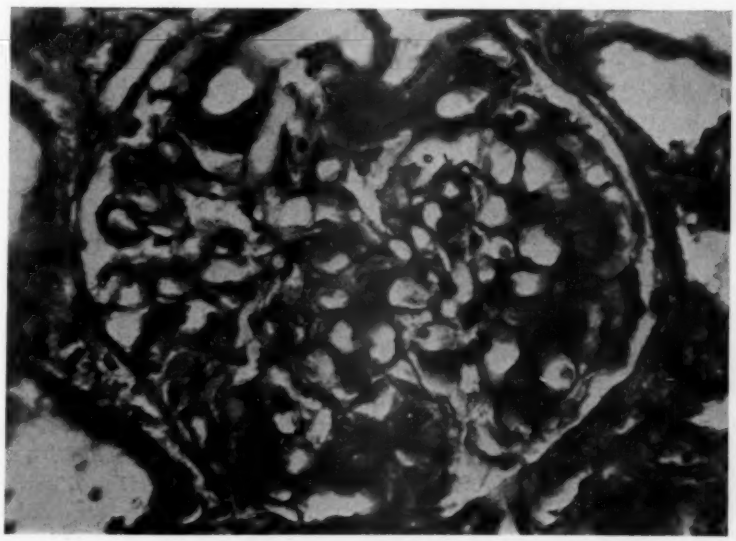


Fig. 4.—Kidney showing amyloidosis. (Magnification × 360.)

CASE 2.—S., a 15-year-old Hindu girl, complained of chronic cough for 8 years, diminution of visual acuity for 4 years, enlargement of cervical lymph glands for 1 year, feeling of tightness and pain in all the limbs, and edema of the feet for 1 month. The patient's father said that she was becoming more and more irritable day by day. She was thinly built, with puffiness of the face, edema of the feet, and some ascites. The cervical lymph glands were enlarged and matted. Both the radial and the brachial pulses were absent. Carotid pulse was present on both sides.

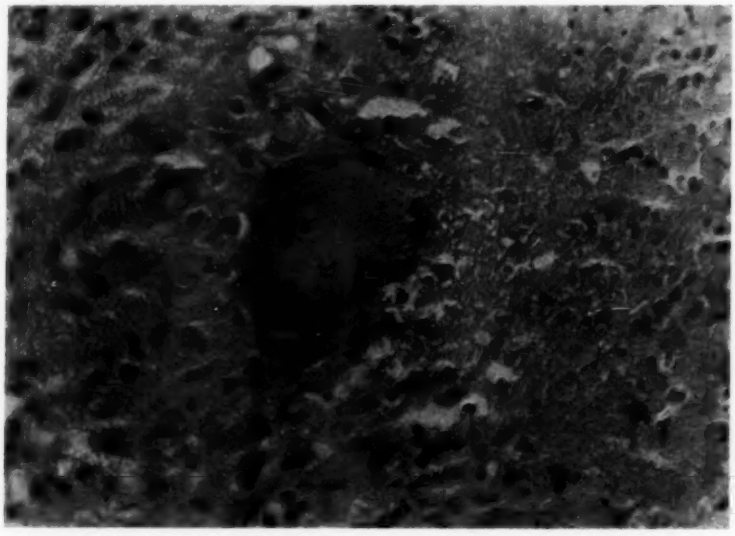


Fig. 5.—Caseating tuberculous lymphadenitis. (Magnification × 360.)

The left femoral pulse was absent, while the right one was palpable. The blood pressure was not recordable in any limb. Urine showed albumin +++, and the microscopic examination was normal. Serum proteins were 4.4. Gm. per cent, with albumin 2.1 Gm. per cent, serum cholesterol 188 mg. per cent, and E.S.R. 22 mm. for the first hour (Wintrobe). The fundus showed highly myopic eyes. The tuberculin test was positive. The Wassermann reaction test was + — —, and the V.D.R.L. test was negative. X-ray of the chest was normal. Lymph-gland biopsy showed caseating tuberculous lymphadenitis (Fig. 5). Left radial arterial biopsy showed normal picture, and kidney biopsy showed amyloidosis (Fig. 6). The patient was discharged from the hospital and is still alive.

COMMENT

This girl is the youngest patient ever reported to have pulseless disease. The clinical picture resembled that of the first case in many respects. In addition to the pulseless condition, she also had cervical lymphadenopathy, which proved to be due to caseating tuberculous adenitis, and a nephrotic syndrome secondary to amyloidosis, which might have been secondary to the caseating tuberculous lymph glands.

CASE 3.—D., a 54-year-old Hindu woman, complained of giddiness for 6 months, especially on exertion, and numbness, tingling, and pain in the left upper arm for 4 months, at times relieved by fomentation and massage. This continued to increase until, incidently, one day the patient herself discovered the absence of pulse in her left arm. For 2 months before admission she started having the same symptoms in her right upper limb, and the right radial pulse became feeble. The left arm was paler and less warm than the right one. At present, the radial and the brachial

pulses are completely absent in both arms. Carotid pulse is present on both sides, and both femoral pulses are faintly palpable. The blood pressure was unrecordable in all four limbs. The patient has bilateral immature cataract, and the fundi are normal. The urine is normal. The E.S.R. is 38 mm. for the first hour (Wintrobe). Serum cholesterol is 335 mg. per cent, the Wassermann reaction and V.D.R.L. tests are negative. X-ray of the chest is normal. On left radial arterial biopsy the intima shows a certain amount of sclerosis, and there is reduplication of the elastic lamina, while the adventitia is normal. There is no occlusion of the lumina with thrombus (Fig. 7). The patient is still alive.

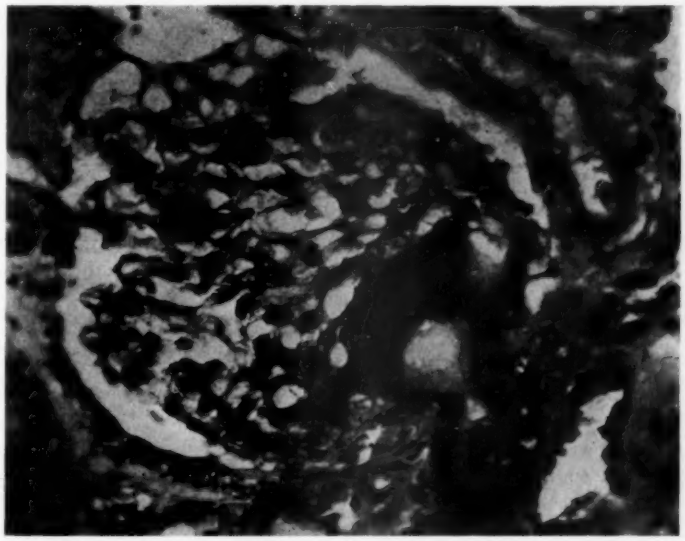


Fig. 6.—Kidney showing amyloidosis. (Magnification × 360.)

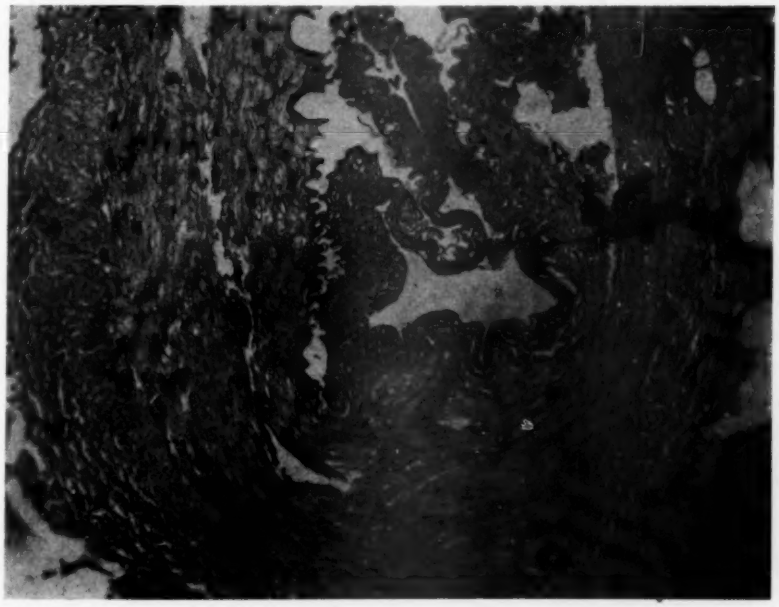


Fig. 7.—Radial artery. Intima showing a certain amount of sclerosis and reduplication of elastic lamina. (Magnification × 80.)

COMMENT

This woman presented chronic progressive obliterative involvement of the radial arteries similar to that in a case reported by Kinney.[5] The bilateral immature cataract is probably due to the deficient blood supply (Ask-Upmark[6]). Giddiness, and numbness and tingling in the left upper limb may be explained as being due to chronic ischemia of the brachiocephalic arteries.

DISCUSSION

Pulseless disease is a curious syndrome of unknown etiology, chiefly affecting young females. Giffin[7] reported the youngest case, aged 19 years, while the oldest case, a 64-year-old woman, was reported by Barker and associates.[8] The basic pathologic change, described by Ask-Upmark,[6] is one of chronic progressive panarteritis of the brachiocephalic arteries, involving all the layers of the arterial wall, along with infiltration of the media with chronic inflammatory cells, mainly the lymphocytes, around the vasa vasora, and eventually leading to obliteration of the arterial lumen. The picture may resemble that of endarteritis productiva proliferans (Frovig[9]), in which there is very little inflammation, but a closure process with organization without evidence of a primary thrombosis. The extent of the pathologic lesion may be variable. It may start immediately at the origin of the three main branches from the aortic arch, obliterating their orifices, but it may also start a few centimeters from their origin. Lesions of the carotid arteries may extend to the base of the skull, but the intracranial branches are spared. In the aorta the infiltration of its walls may be so dense as to suggest a cartilaginous structure. The pathologic tissue has a definite affinity for the arch of the aorta, but may also rarely extend itself into the abdominal aorta, toward the region of the bifurcation, thus affecting the lower extremities. Another outstanding feature on necropsy is the presence of extensive arterial collateral circulation. Renal artery involvement has been described only in two Norwegian necropsies. The renal arteries were normal except for some narrowing at their origin (Raeder and Harbitz[10]). Ask-Upmark[6] in one case found on pyelography that one kidney was of a smaller size. Its diminished size might have been due to primary hypoplasia or to an obstruction of the renal artery with subsequent infarction and organization of the kidney. Barker[8] reported albuminuria ++++ in his case but no histology of the kidney was available to account for this albuminuria.

The symptomatology has been summarized in five categories by Ask-Upmark[6]: (1) Ischemia of the upper half of the body. (2) Signs of collateral circulation. (3) Carotid sinus syncope. (4) Cardiac symptoms. (5) General signs.

1. *Ischemia of the upper half of the body*: Symptoms are found in the arms and in the head, where the arterial insufficiency becomes progressively worse. The arms show rapid exhaustion and pain, chiefly during work with the arms elevated. Easy exhaustion and pain in the jaws while chewing, aged appearance of the face, perforation of the nasal septum, transitory hemiplegia, aphasia or epileptiform fits, and loss of memory, all indicate deficiency of blood supply.

Visual acuity is markedly reduced by walking or other exertion, and returns with rest. Frovig[9] referred to this symptom as visual claudication. Varying stages of cataract formation, corneal opacities, and fundus changes indicate poor ocular circulation. All three of our cases had symptoms referable to chronic ischemia.

2. *Signs of collateral circulation*: The patient may show a vascular systolic murmur which, in most cases, is seen in the angle between the clavicle and the sternomastoid muscle. There may be a continuous machinery-like murmur, as was present in our Case 1 (Lewis[11]). The superficial arteries may be palpable and there may be notching of the ribs.

3. *Carotid sinus syncope*: This has also been reported occasionally.

4. *Cardiac symptoms*: Arterial hypertension has been noted repeatedly in the arteries of the lower limbs, but it is not a constant feature, and a fairly normal blood pressure in the lower limbs has been observed by various workers (Ask-Upmark[6]). Skipper and Flint[12] reported a similar finding. In all of our cases no blood pressure could be recorded in the lower limbs; a similar feature has been reported by Ask-Upmark[6] in one of his cases.

5. *General signs*: The patient may show fever, elevated E.S.R., tachycardia, and negative Wassermann reaction test.

Ross and McKusick[13] reviewed and analyzed about 100 cases. They discussed the whole subject of pulse anomalies under the title of "Aortic Arch Syndrome," and mentioned the various etiological factors responsible for these anomalies: (1) Syphilitic aortitis with aneurysm. (2) Syphilitic aortitis without aneurysm—Motley and Moore[14] reported 7 cases with 3 autopsy reports. (3) Atheromatosis. It is uncommon. (4) Chest injury with or without aneurysm formation. (5) Congenital anomalies. It may be that the anomalous placement of vessels renders them more susceptible to occlusion from any of the above-mentioned causes. Trias de Bes and associates[15] observed mesenchymal abnormalities in their case, indicating a congenital basis for the disease. (6) Thrombophilia—suggested by Nygaard and associates[16] and by Aggeler and associates.[17] (7) Nonsyphilitic arteritis or "young female arteritis," or pulseless disease, or Takayashu's syndrome. There is panarteritis of unknown etiology involving all the layers of the arterial wall, or the picture may resemble that of endarteritis productiva proliferans.

In Case 1 no etiological factor could be determined for the panarteritis which resulted in pulseless disease. Case 2 had caseating tuberculous cervical adenitis and a strongly positive tuberculin test, which might suggest tuberculous etiology of the arteritis in that patient, as suggested by Japanese authors (Kinney[5]), while in Case 3 an elevated serum cholesterol and the radial artery biopsy showing some atherosclerosis suggest much more advanced atheromatosis in the aorta resulting in obliteration of the pulse. Both Case 2 and Case 3 are alive, and therefore a direct histologic examination of the aorta was not possible. Peripheral arterial diseases were excluded in all three of our cases by a radial arterial biopsy.

SUMMARY

Three cases of pulseless disease have been reported, two females and one male. Two of these patients presented an associated nephrotic syndrome due to amyloidosis, a coincidence not reported so far. Etiology and the clinical picture have been dealt with in brief.

We wish to thank Dr. S. P. Tyagi, Dr. K. G. Misra, Dr. R. Uddin, and Dr. H. N. Mehrotra, the house-physicians, for working up the cases, and also Prof. V. S. Mangalik and his colleagues in the Department of Pathology for their reports on biopsy material.

REFERENCES

1. Takayashu, M.: Acta. Soc. Ophth. Jap. **12**:554, 1908.
2. Caccamise, W. C., and Whitman, J. F.: AM. HEART J. **44**:629, 1952.
3. Shikhare, P. V.: Indian J. Med. **2**:326, 1921.
4. Sen-Gupta, S. N., and Ghosh, J. C.: Brit. M. J. **1**:137, 1957.
5. Kinney, J. R.: Am. J. Med. **22**:331, 1957.
6. Ask-Upmark, E.: Acta med. scandinav. **149**:161, 1954.
7. Giffin, H. M.: Proc. Staff Meet. Mayo Clin. **14**:561, 1939.
8. Barker, N. W., and Edwards, J. E.: Circulation **11**:486, 1955.
9. Frovig, A. G.: Acta psychiat. et neurol., Suppl., **39**, 1946.
10. Raeder, J. G., and Harbitz, F. (1926): Cited by Ask-Upmark.[6]
11. Lewis, T., and Stokes, J.: Brit. Heart J. **4**:57, 1942.
12. Skipper, E., and Flint, F. J.: Brit. M. J. **2**:9, 1952.
13. Ross, R. S., and McKusick, V. A.: A.M.A. Arch. Int. Med. **92**:701, 1953.
14. Motley, L., and Moore, R.: J.A.M.A. **100**:656, 1933.
15. Trias de Bes, L., Sanchez Lucas, J. G., and Ballesta Barcons, F.: Brit. Heart J. **27**:484, 1955.
16. Nygaard, K. K., and Brown, A. E.: Arch. Int. Med. **59**:82, 1937.
17. Aggeler, P. M., Lucia, S. P., and Thompson, J. H.: AM. HEART J. **22**:833, 1941.

Rheumatic Heart Disease Associated With Atrial Septal Defect: Clinical and Pathologic Study of 12 Cases of Lutembacher's Syndrome

J. Espino-Vela, M.D., Mexico, D.F.*

The association of mitral stenosis with atrial septal defect (ASD) is currently known as Lutembacher's syndrome.[26] Because our cases reported herein show double mitral lesions and rheumatic involvement of other valves, the designation of rheumatic heart disease (RHD) associated with ASD seems more appropriate. To be sure, other reports labeled as Lutembacher's syndrome have dealt with cases of double mitral lesion associated with ASD, but they are rare.[3,40] Rarer still are reports of involvement of other valves in association with ASD.[17,21,27,35]

It is difficult to decide to whom credit should go for the first description of Lutembacher's syndrome. According to some[37] it goes back to Corvisart, in 1811, over a century before Lutembacher's description. Other reports antedate the classical: Hüter's, in 1864, Martineau's, in 1865, Wagstaffe's,[37] in 1869, Chenieux',[11] in 1870, and Firket's,[17] in 1880. Be this as it may, one thing seems certain, that the incidence of the association is low and that the vast number of reports are concerned with isolated cases.[6,34] We believe that it would be hard to prove that many more than an hundred such instances have been reported.[37] Indeed, some reports deal with nonproved cases, sufficiently suggestive nonetheless of the syndrome. Perhaps the diagnosis is postulated much too often.

From the literature reviewed one is convinced that there is a universal agreement on the fact that the auricular communication must be a true defect or opening of several millimeters in diameter, or perhaps at least one centimeter, and of such a nature as to allow free flow of blood permanently, for the most part, an arteriovenous shunt. Conversely, Bard and Curtillet's syndrome[4] was described as a cyanotic condition in patients whose heart has a .probe-patent foramen ovale (PPFO) which is only capable of allowing a venous-arterial shunt once the pressure in the right auricle exceeds that of the left auricle.[38] Yet, no previous cardiac disease is necessary, and any condition capable of elevating the pressure in the right cardiac chambers, such as pulmonary disease, may

Received for publication Oct. 27, 1958.

*Head of the Department of Congenital Heart Diseases, National Institute of Cardiology, Mexico, D.F.

lead to this syndrome. If a PPFO is present in cases of mitral stenosis, Lutembacher's opinion was that the mitral valve merely acts as an obstacle very much like chronic pulmonary disease. On the contrary, the most prominent hemodynamic feature of true Lutembacher's syndrome is a chronic arteriovenous shunt which leads to right cardiac hypertrophy and pulmonary hypertension; only terminally does the picture become one of inverted shunt through the ASD.

Most of the cases reported describe an ASD that should be classified embryologically as widely patent foramina ovalii. Such, at any rate, is the characteristic of the case of Lutembacher,[26] a defect measuring "3.5 by 4 cm. associated with mitral stenosis."

The present paper deals with 12 proved cases of the association of mitral valvular damage with wide ASD. Embryologically, they seem to be the result of extensive resorption of the septum primum with faulty development of the septum secundum. Three cases had virtually a single auricle[20] (Fig. 4). Although we have encountered half a dozen cases which seem sufficiently characteristic of the syndrome clinically, we have limited this description to 11 cases proved at autopsy and 1 at operation. This seems a relatively high number, and yet it is rather surprising that more cases are not seen since rheumatic heart disease is responsible for no less than 40 per cent of the admissions to the National Institute of Cardiology in Mexico.[9] Likewise, our second most frequent congenital cardiac anomaly is ASD.[16] It is therefore strange not to see these two entities associated more often. Only once in about 500 commissurotomies has the syndrome been discovered at operation, and our surgeons have consistently explored the atrial septum.

A correlation of anatomic findings is made with the clinical, radiologic, and electrocardiographic data. Whenever possible, the size of the auricles was estimated volumetrically. Lung sections were done in 5 cases. Tables I and II summarize the clinical and anatomic findings, respectively.

RESULTS

There were 8 females aged 14 to 71 years, and 4 males aged 10 to 48 years. The mean age for the group was 33.5 years.

With the exception of a 48-year-old man (Case 7) and a 71-year-old woman (Case 12) the clinical diagnosis of rheumatic valvular disease was correctly postulated. A history of rheumatic fever was present in some patients, but Cases 1, 7, 8, 11, and 12 had no such history, and in Cases 6 and 10 it was doubtful (see Table I).

Mitral regurgitation was diagnosed in all but three cases (Cases 7, 11, and 12) because of the presence of a harsh, loud systolic apical murmur radiating to the left axilla; concomitant mitral stenosis was substantiated by the presence of palpable closure of the mitral valve, a snapping first sound at the apex, and, in seven cases, a diastolic rumble without presystolic accentuation. A mitral opening snap was heard in one half of the cases. One had a systolic apical murmur without evidence of mitral stenosis (Case 7). Tricuspid valvular damage was diagnosed in nine cases on the basis of a systolic murmur at the tricuspid area accentuated during deep inspiration (tricuspid regurgitation[32]) (Fig. 2).

Fig. 1.—X-rays of Case 4. There is an important cardiomegaly with profuse vascularity of the lung fields. Notice the prominence of the pulmonary artery, the double contour of the right cardiac border in the frontal view, and the absence of a third left arch, i.e., apparently, no left auricular enlargement. The right oblique view shows no enlargement of the left auricle, while the left oblique view might seem suggestive of an elevated left bronchus. Size of the atrial defect is 1.5 cm. in diameter.

TABLE I

CASE NUMBER SEX, AGE	SYMPTOMS							PALPATION	AUSCULTATION							
	RHEUMATIC HISTORY	DYSPNEA ON EFFORT	ORTHOPNEA	PAROXYSMAL DYSPNEA	COUGH	HEMOPTYSIS	CYANOSIS	THRILL	SNAPPING APICAL FIRST SOUND	SYSTOLIC MITRAL MURMUR	MITRAL OPENING SNAP	ATYPICAL DIASTOLIC RUMBLE	ACCENTUATED P_2	PULMONARY AREA MURMURS	TRICUSPID AREA MURMURS	AORTIC AREA MURMURS
1. (1962) F, 55	No	+++	No	No	No	No	No	?	Yes	Yes	No	None	Yes	No	Systolic	No
2. (572) F, 15	Yes	+++	Yes	No	Yes	Yes	No	Apical and basal	Yes	Yes	Yes	None	Yes	Systolic	None	No
3. (510) M, 10	Yes	+++	Yes	No	Yes	Yes	No	Apical and basal	Yes	Yes	Yes	Yes	Yes	Systolic and diastolic	Systolic	No
4. (5556) M, 20	Yes	+++	No	No	Yes	Yes	Yes	Apical	No	Yes	Yes	Yes	Yes	Systolic	Systolic	No

5. (46277) F, 33	Yes	+++	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Systolic	None	No
6. (10282) M, 21	?	+++	Yes	Yes	Yes	Yes	Apical and basal	No	Yes	?	Yes	Systolic	Systolic	Systolic and diastolic
7. (2979) M, 48	No	+++	No	No	No	No	Basal	No	Yes	No	None	Yes	Systolic	None	Systolic
8. (53249) F, 32	No	+++	Yes	Yes	No	Yes	Apical and basal	Yes	Yes	Yes	Yes	Yes	Systolic	Systolic	No
9. (22814) F, 27	Yes	++	Yes	No	Yes	No	Apical	Yes	Yes	Yes	Yes	Yes	Systolic	Systolic	No
10. (56609) F, 56	?	+++	Yes	No	No	No	Apical	No	Yes	No	Yes	Yes	Systolic	Systolic	No
11. (58484) F, 14	No	+	No	No	Yes on effort	No	No	Yes	No	No	None	Yes Split	Systolic	No	No
12. (60983) F, 71	No	+++	Yes	No	Yes	Yes	±	No	Yes	No	No	Yes Split	No	No	No

Aortic valvular involvement was suspected premortem in only one case, because of the presence of an aortic diastolic murmur. Auricular fibrillation was present in 3 patients, Cases 5, 8, and 12, aged 33, 32, and 71 years, respectively. The only living case had chronic protracted auricular flutter. Other pertinent findings were systolic and diastolic apical thrills in one patient despite the fact that

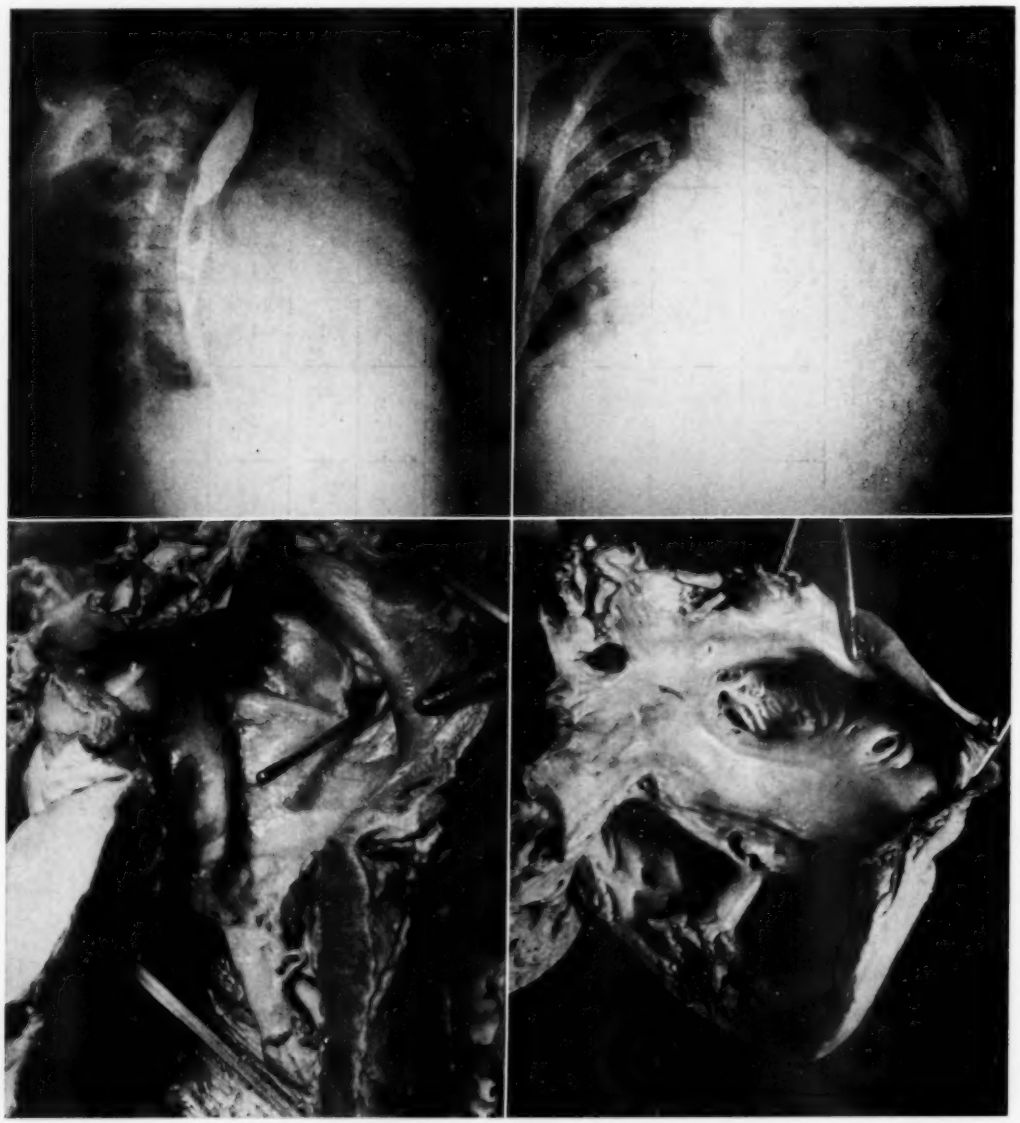


Fig. 2.—X-rays, electrocardiogram, and specimen of Case 6. Notice in the x-rays that there is no conspicuous prominence of the pulmonary artery despite vascularity of the lungs. The right oblique view shows a slight but seemingly evident left auricular enlargement. Below, the specimen seen from the left cardiac chambers (left). Notice the auricular septal defect, which in the fresh specimen measured 2 cm. in diameter; the mitral stenosis was so severe that the papillary muscles are fused with the mitral valve leaflets, and no chordae tendineae remain visible. To the right, the heart is seen from the right cardiac chambers. Notice here the severe tricuspid damage; here too, chordae tendineae have practically disappeared. The electrocardiogram shows a right axis deviation, a right bundle branch block, extrasystoles, and a notched P wave in Lead I.

no accentuation of the diastolic rumble was heard. A systolic impulse at the second left intercostal space and a palpable closure of the pulmonic valve were frequently found. Forceful heave of the precordial area was present in the younger patients (Cases 2 and 3). A systolic impulse at the lower sternal area was the rule. Finally, the maximal apical impulse was invariably displaced to the left and downward. One patient had hypertension in the upper extremities and hypotension in the lower extremities, that is, evidence of aortic coarctation (Case 7); his intercostal arteries were palpable. Clinical and laboratory data of active rheumatic fever were present in Cases 2 and 3 and for some time in Case 9. The suspicion of mitral damage in Case 11 was based solely on the presence of a snapping first apical sound and a faint apical rumble. The ASD was readily diagnosed. Case 12, the 71-year-old patient, was thought to have advanced cardiosclerosis and chronic cor pulmonale.

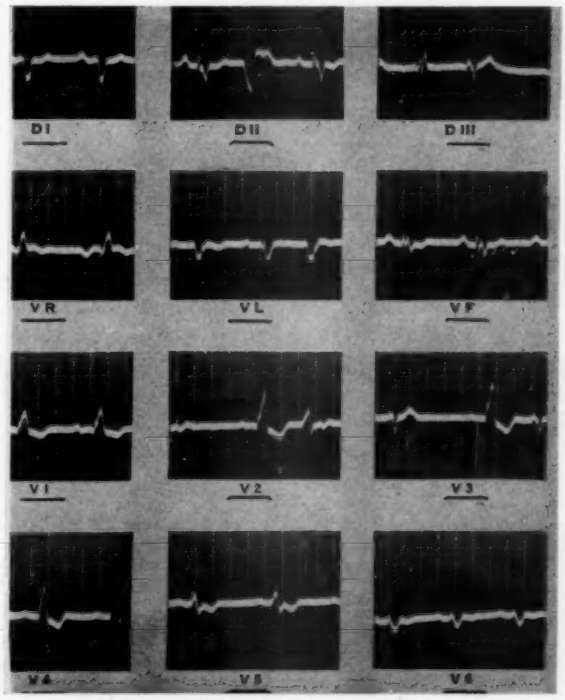


Fig. 2.—ECG. *(For legend see opposite page.)*

Radiologic examination either substantiated or was compatible with the diagnosis of rheumatic heart disease in every case: the cardiac shadow was consistent with mitral, mitral and tricuspid, or mitral-tricuspid-aortic valvular heart disease. The pulmonary segment in some cases (Fig. 4, Case 8) was very prominent. In others (Fig. 2, Case 6) it was not especially prominent; it formed a large convex contour continuous with the arc of the right ventricle. This was felt to be due to considerable clockwise rotation of the heart, with the pulmonary artery displaced toward the back. The pulmonary branches were usually large and opaque; frequently, circular patchy areas of profuse vascularity were seen

in the lung fields (Figs. 1, 3, and 5), even in cases in which the middle arc was not very prominent. The pulmonary artery and the hilar shadows had increased pulsations, a true hilar dance. The left auricle was not enlarged in several cases, but in some this chamber was definitely, although slightly, enlarged (Figs. 2 and 5) as judged by the displaced barium-filled esophagus. By and large, the important cardiomegaly commonly seen made it difficult to evaluate the true degree of left auricular enlargement.

TABLE II. ANATOMIC FINDINGS

CASE	MS	MR	TS	TR	AS	AR	DIAMETER OF ASD	OTHER FINDINGS
1. (1962)	+++	++	−	+	−	−	Single auricle	
2. (572)	+++	++	−	−	−	−	Very large	Hypoplastic aorta; acute glomerulonephritis
3. (510)	++	+	±	+	±	+	1.5 cm.	
4. (5556)	++	++	−	−	−	−	1.5 cm.	
5. (46277)	++	+	−	±	+	−	2.5 cm.	
6. (10282)	++++	+	+	+	+	+	2.0 cm.	
7. (2979)	++	+	−	−	−	−	3.5 cm.	Aortic coarctation; fenestrated aortic valves
8. (53249)	+++	++	±	±	−	−	5.0 cm.	
9. (22814)	++	+	−	−	−	−	6.0 cm.	Patient operated for mitral stenosis only
10. (56609)	+++	+	±	±	−	−	4.5 cm.	
11. (58484)	++	+	−	Functional	−	−	Sutured defect: size of suture, 24 mm.*	Mitral area 1.84 cm.^{2} (postmortem)
12. (60983)	++	+	−	Functional	−	−	3.5 cm.	

*This patient was operated upon under hypothermia for closure of the ASD; she died suddenly of cardiac standstill at the completion of the surgical procedure.

MS = Mitral stenosis. MR = Mitral regurgitation. TS = Tricuspid stenosis. TR = Tricuspid regurgitation. AS = Aortic stenosis. AR = Aortic regurgitation.

The right auricle was always very large, and it formed most of the right arc of the right cardiac border (Figs. 1, 2, and 3). The right ventricle was likewise greatly enlarged in contrast with the left one, which was moderately enlarged despite the presence of a double mitral lesion in some cases. Again, its true size was difficult to estimate. The aorta was usually normal or even hypoplastic, even in cases with aortic valvular damage. It was normal-looking in a case associated with aortic coarctation (Fig. 3). This case showed rib-notching.

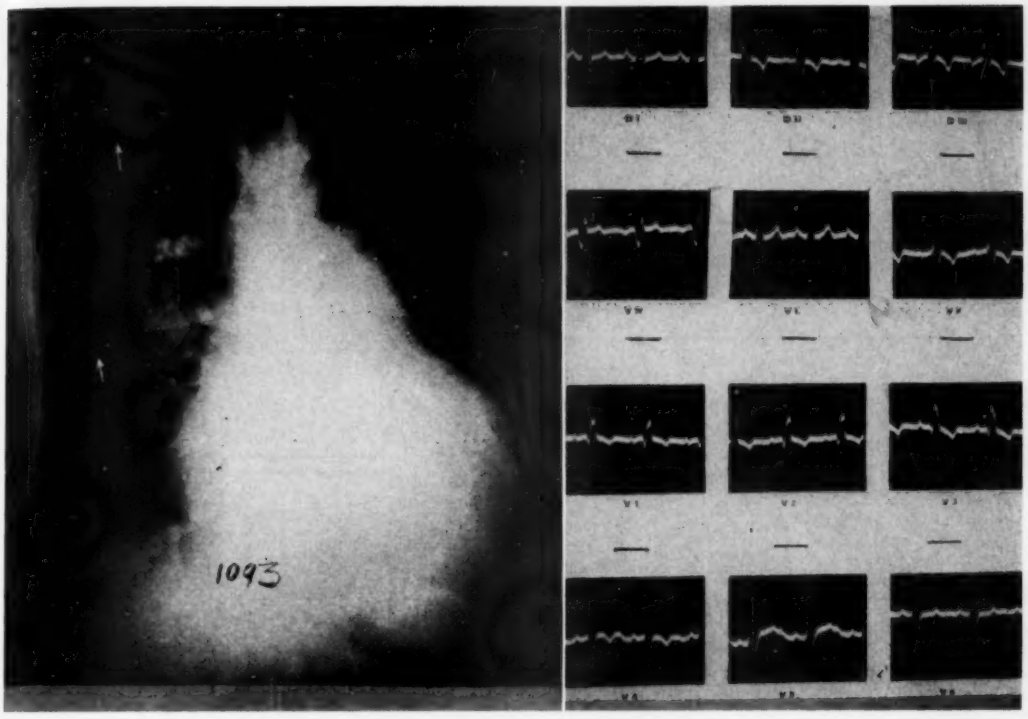


Fig. 3.—X-ray and electrocardiogram of Case 7, the patient who had a double mitral lesion and aortic coarctation. Notice some of the notches in the ribs (indicated by arrows). The atrial septal defect measured 3.5 cm. in diameter.

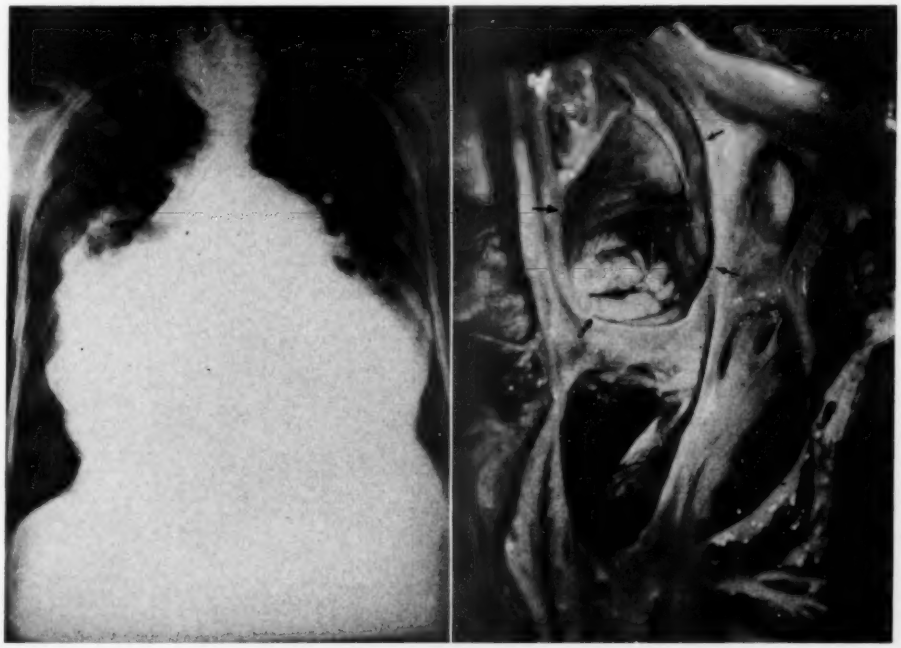


Fig. 4.—Frontal x-ray of Case 8 and specimen. Notice the huge cardiomegaly with profuse vascularity of the lung fields. The atrial septal defect is huge—practically a single auricle (indicated by the arrows). Through this defect is seen the slit-like orifice of the stenotic mitral valve.

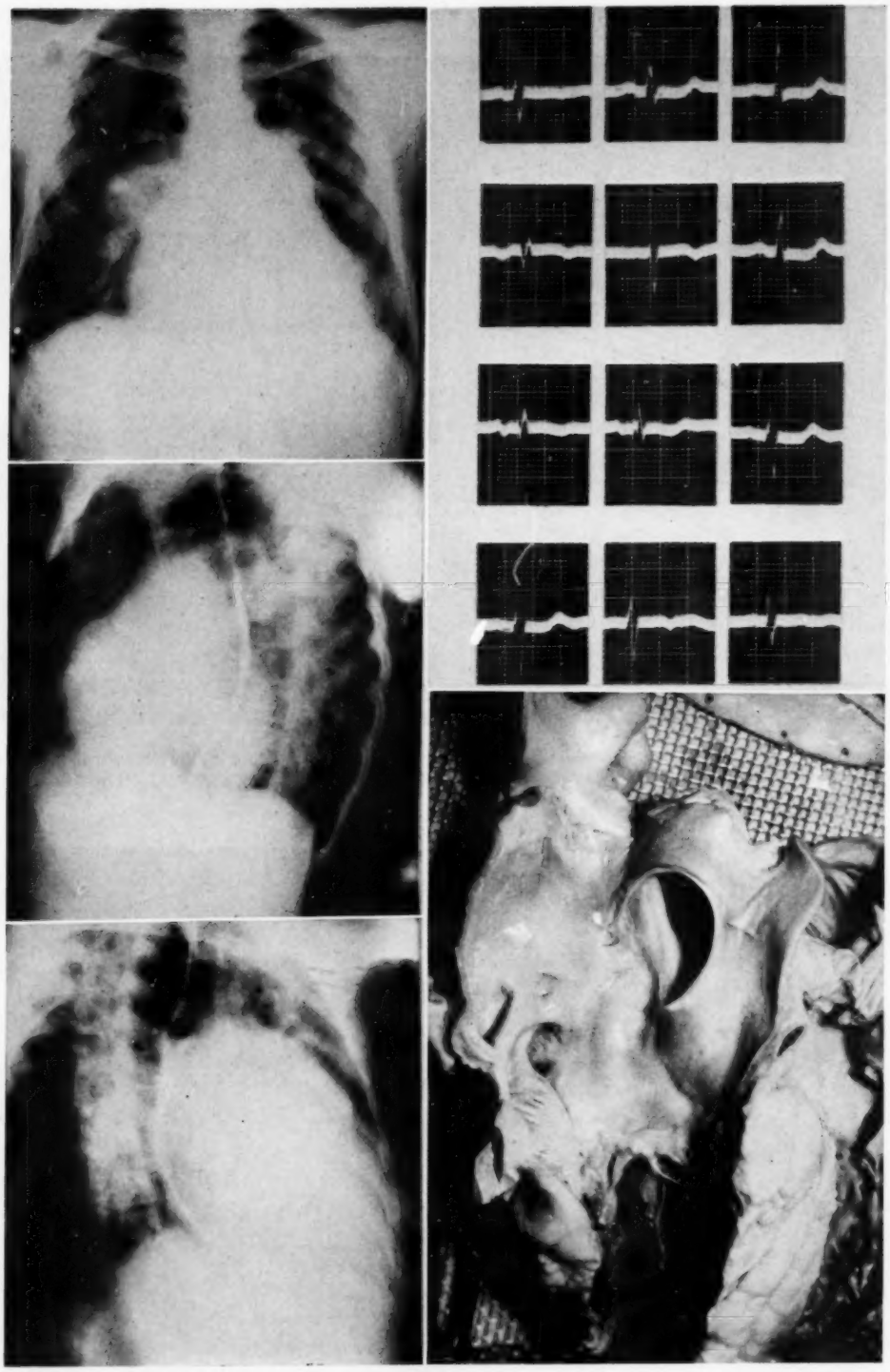


Fig. 5.—X-rays, electrocardiogram, and specimen of Case 10. Notice in the x-rays that cardiomegaly is not particularly large. Prominence of the pulmonary artery and vascularity of the lungs is, however, quite conspicuous. It is very difficult to ascertain the true size of the left auricle, since there is some amount of rejection of the barium-filled esophagus by the left auricle in the right oblique position; yet, in the left oblique position the left bronchus is not displaced upwardly by the left auricle. The electrocardiogram shows a right axis deviation, a notched "mitral" P wave, and a right bundle branch block. The picture of the specimen shows a very large defect, measuring 4.5 cm. in diameter; notice also the thickening of the free edge of the tricuspid valve leaflet and the chordae tendineae.

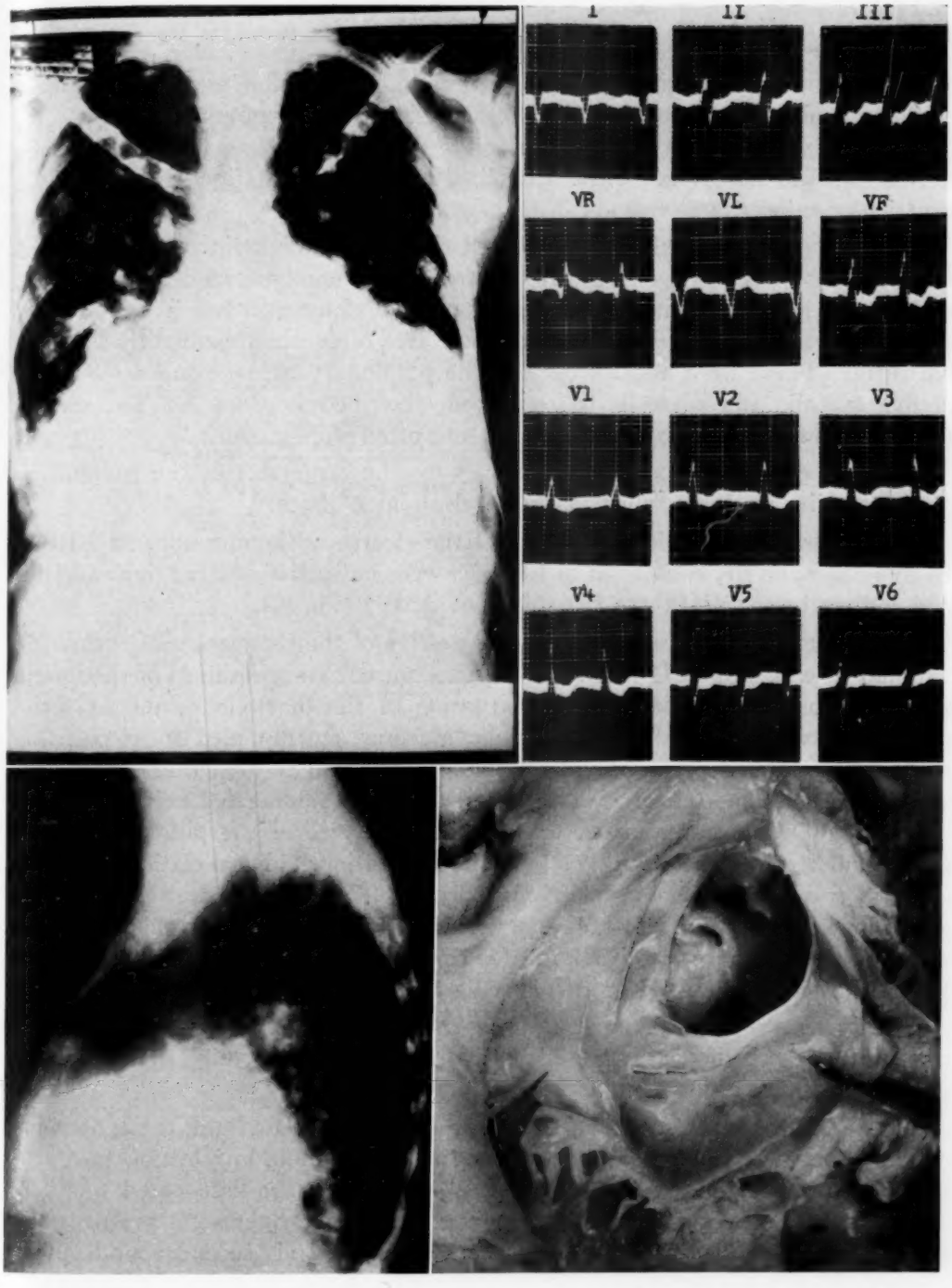


Fig. 6.—X-rays, electrocardiogram, and specimen of Case 12, a 71-year-old woman. Cardiomegaly is very apparent; profuse vascularization of the lung fields is evident. The left lateral view does not show displacement of the bronchus nor backward displacement of the esophagus by the left auricle. The specimen shows a slightly enlarged left auricle. The defect is huge; it measured 3.5 cm. in diameter. Notice the thickening of the valve under the defect. Portions of the leaflet have been removed; they had evidence of rheumatic damage. The electrocardiogram shows a right axis deviation, auricular fibrillation, and right ventricular hypertrophy; qR complexes in the right precordial leads bespeak considerable right auricular enlargement.

Electrocardiographically there were signs of right ventricular overloading, as was to be expected in mitral valvular disease. In addition, every case showed a right bundle branch block (RBBB) with polyphasic complexes of the qR, rsR, or W type in Lead V_1. The P wave was often enlarged and sometimes showed marked notching. Three cases had auricular fibrillation (Fig. 6). Left ventricular enlargement was not infrequent.

The diagnosis of ASD was suspected clinically in eight instances. One of the orienting signs was cyanosis. It was doubtful in one case, moderate in seven, and absent in the remainder. Other supportive elements were, in ten cases, a moderate systolic murmur at the pulmonary area often accompanied by a palpable thrill. There were no murmurs at the pulmonary area in one case, and a double systolic and diastolic murmur was described in Case 3. The second pulmonic sound was always accentuated and often widely split.

Radiologic data suggestive of ASD were the large size of the pulmonary artery and its branches, with marked pulsations of both.[33]

In support of the diagnosis of ASD the electrocardiogram showed RBBB. In five cases the qR complexes of Lead V_1 were indicative of large right auricles and indirectly suggested the possibility of ASD[36] (Fig. 6).

In summary, the clinical features suggestive of the association of rheumatic valvular disease and ASD were: (1) atypical auscultatory findings of rheumatic mitral stenosis: no presystolic accentuation of the diastolic rumble; (2) the presence, quite commonly, of a systolic murmur accompanied by a palpable thrill in the pulmonary area; and (3) cyanosis of slight to moderate degree (not seen in the absence of heart failure). Radiologically, supportive evidence of the diagnosis of this association were: (1) the large size of the pulmonary main trunk and its branches, with (2) vigorous pulsations, in association with (3) a mitral or mitral-tricuspid cardiac contour, and (4) slight or absent left auricular enlargement. Finally, electrocardiographic data suggestive of this diagnosis were: (1) the presence of RBBB and (2) commonly, qR type complexes in Lead V_1 with (3) concomitant left auricular enlargement ("mitral" P waves).

Two cases were catheterized: Cases 9 and 11. The results of catheterization in Case 9 are shown in Table III. Notice the relatively high pressure within the left auricle and the pulmonary vein.

Case 9 was also studied phonocardiographically; the findings at the apex included a mitral opening snap and a mid-diastolic rumble in addition to a systolic murmur. The interval between the Q wave and the first sound was 0.09 second. At the pulmonic area there was a muffled first sound, a protosystolic snap, a rather loud systolic murmur, and a widely split second sound. This patient eventually underwent commissurotomy, with the correct diagnosis of Lutembacher's syndrome. The ASD found at operation measured approximately "6 by 6 cm. in diameter." It was felt safer to perform a second operation by right thoracotomy and with a plastic patch. The patient has refused to be operated upon for closure of her defect because she obtained relief through commissurotomy (alleviation of cough and dyspnea). The stenotic valve measured 1 $cm.^2$.

Course.—The disease progressed with increasing dyspnea: orthopnea and even paroxysmal dyspnea in some cases. Cough and hemoptysis were present in several patients (see Table I). Finally, nine patients died in severe congestive cardiac failure, some of these with active rheumatic fever, i.e., the younger patients, and some, very late in life (Case 12). Case 10 was being treated for mild cardiac failure at the age of 56 years. She died of acute renal failure from an excessive dose of mercurial diuretic administered by mistake. Case 11 died immediately after completion of closure of the ASD. Case 9, the living patient, is in mild chronic failure and requires digitalis in small doses.

TABLE III. CATHETERIZATION DATA IN CASE 9

SITE	GAS ANALYSIS		PRESSURE (MM. Hg)		
	VOL. O_2	SATURATION (%)	SYSTOLIC	DIASTOLIC	MEAN
SVC	13.28	76.71	—	—	—
RA	15.85	91.40	—	—	10
RV	14.50	83.89	54.0	4	22
PA	14.78	85.30	54.0	20	35
LA	15.29	88.20	—	—	12
PV	16.50	—	—	—	20
FA	15.84	91.40	—	—	

Capacity 17.34%
Hemoglobin 12.9 Gm.

SVC = Superior vena cava. RA = Right auricle. RV = Right ventricle. PA = Pulmonary artery. LA = Left auricle. PV = Pulmonary vein. FA = Femoral artery.

Pathology.—The heart was always enlarged, ranging in weight from 540 to 740 grams. The most dilated cavity was the right auricle, followed by the hypertrophied right ventricle and the left ventricle. The left auricle was slightly enlarged or normal, its volume being calculated approximately at between 37.5 c.c. for the smallest case and 100 c.c. for the largest. According to standard volume measurements in Mexico, by Velazquez,[42] a few cases exceeded normal figures.

The ASD was thought to be so large in three cases as to constitute virtually a single auricle. The measurements of the defect in the remainder varied between 15 and 60 mm. in diameter (see Table II).

The rheumatic attack was generally severe and, in the majority of instances, extensive, with variable degrees of rheumatic activity. Double mitral lesions were present in all, with predominating mitral stenosis. Tricuspid involvement was severe in two cases and mild to moderate in five other cases; regurgitation was prevalent. Aortic damage was seen in three cases, but was always slight.

Evidence of old pulmonary infarcts was found in one case. An adult type of coarctation was present in Case 7. Case 2 showed pathologic evidence of acute glomerulonephritis.

The pulmonary artery was always considerably larger than the aorta. It showed calcified atheromatous plaques in some cases.

DISCUSSION

While some workers[5,8,18,37,38,39] admit the congenital nature of the mitral lesion, all of our cases, including the clinical case (on which biopsy of the right auricular appendage showed a healed rheumatic endocarditis), are unquestionably pathologically proved examples of rheumatic heart disease. A true history of rheumatic fever or of rheumatic activity was a strong point in favor of this diagnosis in at least five cases. Lutembacher's original case and several cases reported in the literature have had no history of rheumatic fever.[2,3,5,8,13,17,22,24,26,31,39]

Outstanding manifestations in this syndrome are those which express pulmonary hypertension as a repercussion of the association of rheumatic heart disease and ASD. Either of these entities separately tends to elevate pulmonary pressure. It could be advocated theoretically that they combine their effects when they coexist.[24,41] In many of our patients there was clinical, radiologic, and electrocardiographic evidence of pulmonary arterial hypertension. More important, however, were the clinical manifestations of capillary venous hypertension observed in several of these patients, such as orthopnea, hemoptysis, and paroxysmal dyspnea. Orthopnea is seen in accentuated mitral stenosis in the absence of cardiac failure. Paroxysmal dyspnea and hemoptysis perhaps indicate that in addition to increased capillary venous pressure there was a relatively weak arteriolar vasoconstriction, incapable of constituting a "defensive barrier" to the venous capillaries. Some reported cases have had similar venous capillary hypertension, including hemoptysis.[11,23,37] Another explanation for this might be the difficulty encountered by the left auricle in emptying its contents into the left ventricle through the stenotic mitral valve and through the ASD into a hypertensive right auricle. Both factors may add their effects. That hemoptysis may have other causes than venous capillary hypertension is beyond question. Yet when it coexists with severe chronic dyspnea, it is suggestive of venous capillary hypertension.

Pulmonary arterial hypertension may be masked clinically during a certain phase of the disease by the presence of tricuspid damage,[10] since tricuspid regurgitation often leads to "pulmonary decongestion" and improvement of symptoms which express pulmonary engorgement. For this reason it may be valuable to discover hemoptysis in patients who, like ours, had tricuspid regurgitation. One is almost forced to admit that despite the presence of this "decongesting" lesion,[1] hypertension due to the hemodynamic disturbance caused by ASD added its effects to those of hypertension due to mitral stenosis. Yet, it must be borne in mind that tricuspid regurgitation in mitral stenosis expresses greater pulmonary pressure.[1,10]

An opposite view maintains that the presence of ASD is a protective mechanism against pulmonary hypertension in mitral patients, by acting favorably on the venous capillary network. In other words, this segment of the pulmonary circuit in a patient with mitral stenosis would be better protected when an ASD is present. This original view was first postulated by Firket,[17] in 1880. Lutembacher[26] was of the opinion that because of the presence of ASD, the danger of pulmonary stasis in mitral stenosis is diminished, and that stasis begins in the lungs and ends in the systemic circulation; conversely, cases with added

ASD begin with stasis in the systemic circulation and end with pulmonary engorgement—possibly due to inverted shunt at the auricular level. We found little evidence to support this view in several of our cases. This may be due to the fact that the smaller the area of the ASD the more resemblance there is to pure mitral stenosis without ASD. Five cases, two of which showed virtually a single auricle and three a defect of at least 35 mm. in diameter, did not have the symptoms of venous capillary hypertension such as severe dyspnea and hemoptysis. Two more cases (Cases 11 and 12) had slight mitral stenosis with a large ASD. The remainder had a smaller ASD.

With regard to diagnosis, from the auscultatory point of view, it is significant that the diastolic apical rumble was always atypical, as pointed out by Lutembacher[26] and later by others.[2,19,24] Lutembacher's explanation seems adequate: the blood entering the left auricle follows two paths, and the small amount of blood traversing the stenotic mitral valve is incapable of producing a typical diastolic rumble with presystolic accentuation. Although this author's original case was in heart failure and had auricular fibrillation, there do not seem to be good reasons to invalidate his findings nor his interpretation. In our series there were cases with sinus rhythm and others with auricular fibrillation. Auscultation did not differ in either group in this respect. It is well to add that all our cases had more than one type of valvular lesion, and this is an important difference from true Lutembacher's syndrome. Not always is auscultation as described. Some cases in the literature[7,30,37] have had a typical Duroziez murmur accompanied by a diastolic apical thrill. The presence of a systolic murmur at the pulmonic area seems a good aid in the diagnosis, although it is not specific; it expresses pulmonary dilatation, a quasi-constant feature in ASD.

The presence of cyanosis was a useful clue in suspecting ASD in five of the cases. This sign is the consequence of pulmonic hypertension,[14] but it was always present in advanced stages of the disease. It must be severe or one runs the risk of attributing too much value to it in cases in which rheumatic valvular lesions are capable of causing it through peripheral circulatory stasis in the absence of ASD. We have seen this to be true in chronically ill mitral and tricuspid patients,[1] in ventilatory insufficiency[5] of mitral patients reaching the stage of chronic cor pulmonale[12] with slight to moderate unsaturation and peripheral cyanosis.[26] While hypertension antedates cyanosis, it is also its cause, so that at some stage there may be mixed shunts,[15] which later become predominantly inverted. Finally, severe congestive heart failure, the final stage of cardiac reserve, was apparently the result of several factors, among which pulmonary hypertension was outstanding in nine autopsy cases. The living patient, 27 years of age, has no evidence of cyanosis or unsaturation (91 per cent arterial saturation is within normal for Mexico City); her pulmonary pressure was 54 mm. Hg. Nor was cyanosis seen either in the patient who died accidentally (Case 10), and it was very mild in the 71-year-old patient (Case 12) who had led an active life and had had several pregnancies. Repeated bouts of cardiac failure are not uncommon prior to death. They were seen in this series and in others reported.[2,31] The severity of rheumatic activity seems important in the rapid course followed by some cases (Cases 2 and 3).

Some workers attribute great importance to radiologic findings for the diagnosis of this entity,[5,8,27,33] the most salient points being the large size of the pulmonary artery and its branches with vigorous pulsations, especially in the presence of a cardiac shadow which is reminiscent of mitral valvular disease. Such findings indicate the increased flow through the pulmonary circuit, which is, for the most part, arteriovenous during a long period of the patient's life, before great pulmonary hypertension, cardiac failure, and inversion of the shunt take place. The outline of the left auricle is important. There would seem to be reasons to believe that it should be normal in size or slightly enlarged. This would be in agreement with the view of the protective role of the ASD. Here again, as with clinical features, the protective role of the ASD seems true only for some cases; for others in our series this chamber was enlarged.[23] This enlargement may be seen only in the left anterior oblique view, but occasionally it is seen as a double contour in the frontal view (Fig. 1). A third arc in the frontal view was not seen. This seems a good negative diagnostic feature. It was not easy to correlate the size of the left auricle with the size of the ASD; one case with a large ASD seemingly had a large left auricle (Fig. 5).

The electrocardiograms are certainly compatible with the diagnosis of mitral valvular disease with right ventricular hypertrophy. The presence of polyphasic complexes, indicative of RBBB, is not uncommon in mitral valvular disease complicated by tricuspid damage; it is a highly frequent finding in ASD.[25,43] Therefore, it is sometimes difficult to attribute this sign to either disease individually considered. It was seen in three autopsy cases without tricuspid involvement. The morphology of the P wave seems important: it is usually wide, and deeply notched. This is in perfect agreement with the diagnosis of a "mitral P wave" despite the fact that some cases had a doubtful left auricular enlargement.

Pathologically, the right auricle was the largest chamber in several specimens. The left auricle varied in size from slightly enlarged to normal, which is in agreement with radiologic findings. Cases in which this chamber was large may suggest that the ASD was insufficient to protect it from hypertension[29] because of its small size. But this is not invariably the case. Histologically, some changes in the arteriolar pulmonary vessels and in the pulmonary artery were expected. Widely dilated pulmonary arteries were found. But lung sections from five cases did not reveal important vascular arteriolar damage. This is not remarkable since we have not been able to find any more than slight changes even in severe mitral patients without ASD.[28]

SUMMARY AND CONCLUSIONS

Twelve proved cases of the so-called Lutembacher's syndrome are presented, eleven at autopsy and one at operation. The relative rarity of this disease is emphasized, considering that ASD is the second most frequent congenital cardiac malformation in Mexico City, and that cases of rheumatic heart disease make up over 40 per cent of the admissions to the National Institute of Cardiology in Mexico. In every case myocardial rheumatic valvular disease

was severe and extensive, quite often affecting more than one valve. This rules out the congenital nature of the mitral stenosis.

Clinically, the disease is most often typical of severe rheumatic heart disease, and multiple valvular lesions are the rule. The severity of the lesions described in some of these patients is unlike any descriptions reported. The diagnosis which was commonly and correctly postulated was almost of necessity rheumatic heart disease. The suspicion of the added presence of ASD was based on atypical auscultatory findings, some morphologic and hemodynamic fluoroscopic data of the heart shadow, and the presence of a RBBB in the electrocardiogram. Less often, the diagnosis of ASD was readily apparent while that of rheumatic heart disease was not so obvious (three cases). Two cases were exceptional and neither diagnosis was correctly postulated: one patient had aortic coarctation and another one had lived to the age of 71 years with cardiosclerosis and chronic cor pulmonale.

Physiopathologic considerations are made regarding pulmonary arterial and capillary venous hypertension. A brief comment on the pulmonary vascular histology is made.

REFERENCES

1. Aceves, S., and Carral, R.: Arch. Inst. cardiol. México. **17**:701, 1947.
2. Askey, J. M., and Kahler, J. E.: Ann. Int. Med. **33**:1031, 1950.
3. Balcells Gorina, A.: Medicina clin. **4**:261, 1945.
4. Bard, L., and Curtillet, J.: Rev. méd., México **9**:993, 1899.
5. Bayer, O., Rippert, R., Wolter, H. H., and Loogen, F.: Arch. Kreislaufforsch. **20**:2, 1954.
6. Brugsch, H. G.: Bull. New England M. Center **5**:138, 1943.
7. Courter, S. R., Feson, B., and McGuire, J.: Am. J. M. Sc. **216**:501, 1948.
8. Cramer, A., and Frommel, E.: Arch. mal. coeur **16**:561, 1923.
9. Chavez, I., Robles Gil, J., Ponce de Leon, J., and Chavez Rivera, I.: Arch. Inst. cardiol. México **27**:1, 1957.
10. Chavez, I., Vaquero, M., Mendoza, F.: Arch. Inst. cardiol. México **25**:291, 1955.
11. Chenieux: Bull. Soc. anat. de Paris **21**:22, 1870.
12. Dexter, L.: Arch. Inst. cardiol. México **22**:655, 1952.
13. Dry, T. J.: M. Clin. North America **32**:895, 1948.
14. Duffau, O.: Arch. Hosp. Clin. niños Roberto del Río **14**:189, 1946.
15. Ehni, G., and Grain, L.: J.A.M.A. **150**:1298, 1952.
16. Espino-Vela, J., Mendez-Aponte, J., Aguilar, C., Portillo, B., Pinzon, J., Quiroga, R., and Rubio, V.: Arch. Inst. cardiol. México **28**:174, 1958.
17. Firket, C.: Ann. Soc. méd.-chir. de Liége **19**:188, 1880.
18. Friedberg, Ch.K.: Diseases of the Heart, Philadelphia, 1950, W. B. Saunders Company.
19. Geiger, A. J., and Anderson, H. C.: Am. Heart J. **33**:240, 1947.
20. Griffith, T. W.: Manchester M. Clin. **4**:385, 1902.
21. Huchard and Bergouignan: Bull. et mém. Soc. méd. hôp. Paris **18**:757, 1901.
22. Innerfield, I.: Arch. Int. Med. **85**:490, 1950.
23. Kurz, E. R. H., and Fischer, I.: New England J. Med. **240**:178, 1949.
24. Langeron, P., and Loheac, C.: Paris Med. **51**:545, 1928.
25. Limon-Lason, R., Esclavissat, M., Puech, P., de la Cruz, M. V., Rubio, V., Bouchard, F., and Soni, J.: Arch. Inst. cardiol. México. **23**:279, 1953.
26. Lutembacher, R.: Arch. mal. coeur **9**:237, 1916.
27. McGinn, S., and White, P. D.: Am. Heart J. **9**:1, 1933.
28. Miquel, C., Monroy, G., Espino-Vela, J., and Quijano, F.: El pulmón en los mitrales, Estudio de 23 biopsias pulmonares. (To be published).
29. Pavon-Caballero.: Med. latina **6**:89, 1947.
30. Peco, G., Pastorino, J. C., and Garibotto, R. G.: An. Inst. Clin. Buenos Aires **24**:140, 1943.
31. Purks, W. K.: Arch. Int. Med. **82**:588, 1948.
32. Rivero-Carvallo, M. J.: Arch. Inst. cardiol. México. **16**:531, 1946.
33. Roessler, H.: Arch. Int. Med. **54**:339, 1934.
34. Rossi, S., and Romero, R.: Rev. Med. Hosp. Plata **2**:17, 1945.
35. Sailer, S.: Am. J. Path. **12**:250, 1936.

36. Sodi-Pallares, D., Bisteni, A., and Herrmann, G.: Am. Heart J. **43**:716, 1952.
37. Soulié, P., Bouvrain, Y., and Sibille, A.: Arch. mal. coeur **47**:97, 1954.
38. Souza-Goularte, J. G.: De la stenose mitrale avec communication interauriculaire, Thesis, 1924, Paris.
39. Tinney, W. S., and Barnes, A. R.: Minnesota Med. **25**:637, 1942.
40. Traum, A. H.: M. Bull. Vet. Admin. **20**:274, 1944.
41. Uhley, M. H.: Am. Heart J. **24**:315, 1948.
42. Velazquez, T.: Arch. Inst. cardiol. México. **20**:495, 1950.
43. Vizcaino, M., Vaquero, M., and Pellon, R.: Comunicacion interauricular, Estudio de 20 casos, III Congreso Interamericano de Cardiologia, Chicago, U.S.A., 1948.

Clinical Observations On Coronary Heart Disease in Epidemiological Population Studies

Paul D. White, M.D., Boston, Mass.

INTRODUCTION

The type of research with which this paper deals is but one approach to the problem of coronary heart disease. It should supplement and not replace other kinds of research, that is, the studies concerning this disease in experimental animals, including monkeys, and, when safe, on man himself. Such other studies, of course, should be from all directions, biophysical and biogenetical as well as biochemical, physiological, and clinical (both medical and surgical), and should be carried out preferably by teams combining experts in the various fields.

The epidemiological research to which I refer is still in its early infancy and requires much careful development and encouragement in its growth. It can be done best probably by international teams making comparative studies in various parts of the world, with experts in physiology, biochemistry, nutrition, pathology, and clinical medicine comprising the teams. It is a difficult, time-consuming, and expensive type of investigation.

A pioneer presentation was made in a symposium in Washington at the Second Congress of Cardiology four years ago, and was published later in a small volume by Ancel Keys and myself. It has been the subject of various papers and conferences since, such as that held in Brussels, in September, 1958, by Le Centre d'Étude des Maladies des Artères Coronaires. The present paper is in the form simply of a progress report, quite unfinished, and is presented with the hope that four years from now another such may be possible by myself and/or others, much more advanced but probably still incomplete. This report is an account of my own personal experiences as a pioneer working with many others, and is not intended as an attempt to cover the field and the voluminous literature already printed on the subject.

During the past few years pioneer studies have been initiated among various populations in the Old World and the New in an attempt to determine possible relationships between the ways of life and certain diseases, such as rheumatic heart disease, hypertension, and severe coronary atherosclerosis (in particular,

Presented at the Third World Congress of Cardiology, Brussels, Belgium, Sept. 15, 1958.
Received for publication Oct. 29, 1958.

coronary thrombosis). As further introduction to my subject, I present Tables I, II, and III; the first demonstrates the very great importance of the disease under discussion, and the other two illustrate the complicated picture of the ensemble of the possible causes of the disease in need of investigation.

In the case of coronary heart disease one of the environmental factors or agents that has been not too difficult to measure, and which varies greatly in different parts of the world and in different portions of the same population living in the same place or far apart, is diet. The details of the diet have been and are now, quite rightly, the focus of increasingly intense research, even though it is recognized that other factors such as the degree of physical activity, emotional stress and strain, toxic substances, climate, and especially heredity, also need careful evaluation. If other factors are by nature or by intent essentially constant, it is reasonable to attempt to relate disease or the extent thereof to pronounced variations in the diet. With varying degrees of justification and success such investigations of the diet have been going on in the course of epi-

TABLE I. U. S. PUBLIC HEALTH STATISTICS, 1956

TOTAL DEATHS IN 1956			1,565,000
Diseases of heart and blood vessels			843,410
Coronary heart disease		428,800	
Vascular lesions affecting nervous system, and due in large part to arteriosclerosis		179,110	
General arteriosclerosis		32,420	
Hypertension		84,460	
with heart involvement	73,480		
without	10,980		
Other types of cardiovascular diseases, including rheumatic, congenital, etc.		118,620	

TABLE II. HOST: BASIC FACTORS BEHIND CORONARY HEART DISEASE

1. Race
2. Heredity
   - A. Physical characteristics
     - a. Body build
     - b. The coronary arteries themselves
       1. The wall itself
       2. The tree and its anastomoses
   - B. Chemical and metabolic
     - a. Diabetes
     - b. Hypercholesterolemia
     - c. Other
   - C. Nervous, mental and spiritual, including the sensitivity of the patient. Personality and character
3. Age
4. Sex
5. X

demiological pioneering. At the same time it is to be recognized that similar pioneering should proceed in the appraisal of other environmental factors.

It has been my good fortune, inasmuch as I have long been interested in the pathogenesis and etiology of coronary heart disease, to have been invited to join in some of the team researches of two of the present-day authorities in the study of nutrition as it relates to diseases such as coronary thrombosis. These pioneers in national and international epidemiological research are Professor Ancel Keys, of the University of Minnesota, and Professor Fred Stare, of Harvard University.

A summary review of my clinical experiences with these observers and with others during the past few years appears to be worth while, both for the information already derived and as a background for further and more extensive and intensive investigations. I should like to express my appreciation to my fellow clinical observers in these various researches, including especially the following: Drs. Malmros and Biörck, of Sweden, Drs. Puddu, Mattioli, Posteli, and Poppi, of Italy, Dr. Kimura, of Japan, Dr. Bronte-Stewart, of South Africa, Dr. Carlotti, of France, and Drs. Levine, Sprague, Bland, Lerman, Gertler, Garn, Pomeroy, Berman, Larsen, and Miller, of the U.S.A., as well as to the many experts in the fields of biochemistry, physiology, and nutrition from those and other countries (England, Finland, Austria, Yugoslavia, and Greece) who have carried out the clinical laboratory studies. I would like also to thank Professors Sotgiu, of Bologna, Caccuri, of Naples, Aresu, of Cagliari, and Ellis, of Boston, for their help in arranging some of these studies.

TABLE III. AGENT: SECONDARY OR ENVIRONMENTAL FACTORS BEHIND CORONARY HEART DISEASE (THE CHIEF REASON FOR EPIDEMIOLOGICAL RESEARCH)

1. Diet
   - A. Fats
   - B. Proteins
   - C. Carbohydrates
   - D. Total calories
   - E. Vitamins
2. Physical activity or lack thereof
   - A. Work
   - B. Exercise
3. Stress and strain
   - A. The type of strain
   - B. The degree of strain
4. Social customs
   - A. Marital and family status
   - B. Religion (e.g., fasts)
   - C. Social (e.g., siestas, cocktail parties)
5. Toxic substances
   - A. Tobacco
   - B. Alcohol
   - C. Other
6. Parasites
   - A. Bacteria
   - B. Viruses
   - C. Other
7. Climate and weather
8. Y

INITIAL STUDIES IN THE UNITED STATES

Although I had been interested for years in efforts to uncover clues as to the cause or causes of serious coronary atherosclerosis, it was only during the last

decade that I personally began to be involved in such studies, first, in the case of 100 persons examined in Boston who had suffered coronary thrombosis under the age of 40 years,[1] and, second, in a follow-up of several hundred Harvard University athletes of a generation earlier who had won their letters playing football.[2]

The 100 cases of coronary thrombosis in young persons[1] included a great preponderance of men; actually, the ratio of men to women was 97 to 3. This was the most important clue in these young adults. The second most important clue seemed to be that of body build. The mesomorph, that is, the broad muscular person, was much more likely to be subject to this disease early than the endomorph or, especially, the ectomorph; in fact, there was not a single pronounced or "pure" ectomorph among the 100 cases. There were a few "pure" endomorphs but many borderline cases, that is, mesomorphic-endomorphs and ectomorphic-mesomorphs. The third clue was that of family history. There was definitely more coronary heart disease in the immediate ancestors of the coronary cases than in the ancestors of a control series. The fourth clue was that of the serum cholesterol which, although varying widely, averaged a definitely higher figure in the cases of coronary thrombosis, and in a few of those the figure was very high. Other factors such as diet, exercise or lack thereof, the use of tobacco and alcohol, and stress and strain were less clear in their relationships, probably due in large part to their uniformity.

A study of the football players[2] was much less satisfactory, partly because it was largely in retrospect by questionnaires, and partly because the average American college graduate lives in much the same way as his fellows after graduation. Football players were chosen in this study because they were almost all of the mesomorphic build, and, therefore, in that particular, nearly all candidates for coronary heart disease. Four hundred and twenty-four Harvard College students who had won their football "H" from 1901 to 1930 inclusive were followed up. A considerable number of these were able to supply too little useful information, but for the analysis of certain data there was adequate knowledge about 355 persons. The chief cause of death among those who had died was coronary heart disease, which was responsible in 25 cases, or 29 per cent of the 87 deaths, out of the total series of 355 cases. Cerebral "hemorrhage," generalized arteriosclerosis, and congestive heart failure accounted for 8 more deaths, making a total cardiovascular mortality of 33 cases or 38 per cent. Cancer ranked second, causing 11 deaths or 13 per cent. Pneumonia and war injuries accounted for 9 deaths or 10 per cent each, accidents for 8 deaths or 9 per cent, suicide for 4 deaths or 5 per cent, and typhoid for 2 deaths. Death in the remainder of the cases (13 per cent) was due to miscellaneous diseases. Meanwhile, the male white population of the same age in 1940, in Massachusetts, showed cardiovascular deaths amounting to 44 per cent, while cancer caused 13 per cent, accidents 7 per cent, pneumonia 5 per cent, and other causes accounted for 31 per cent; it was, however, impossible to determine just how many of the cardiovascular deaths were of coronary origin in the general population.

Among these football players there was a higher percentage of positive family history of coronary heart disease in the coronary group than in the controls. The coronary group included 9 living cases as well as the 25 who had already

died of coronary heart disease. One of the most significant findings in the study was the apparent protection afforded by the continuation of a program of heavy exercise. It happened that no individual in this study who had maintained a program of heavy exercise throughout life had as yet developed evidence of coronary heart disease.* Neither tobacco nor alcohol appeared to have much influence on the development of coronary heart disease. Unfortunately, the lack of detailed and accurate information about the dietary habits prevented any satisfactory conclusions as to diet in this particular group.

The chief defects revealed in a study of this sort lie in its retrospective nature and in the uniformity of the ways of life of most Harvard or other college graduates, and, therefore, in the difficulty of comparing extremes because of the inadequate numbers represented therein. Dr. Pomeroy and I,[2] in a paper recently published in the *Journal of the American Medical Association*, concluded that "a study of racial groups and individuals either in the country of their origin or when transplanted elsewhere, living very differently from others of the same race, should prove much more instructive."

EPIDEMIOLOGICAL INVESTIGATIONS ABROAD

In the spring of 1954, Ancel Keys and his physiological and biochemical associates, Italian, Swedish, and American, carried out a study of four groups of healthy Neapolitan citizens in Italy. The groups were comprised of 138 workers in the Ilva Steel Mills, 150 city firemen, 59 city clerks, and 46 well-to-do citizens who were members of the Rotary Club of Naples. The study included physical examinations, anthropometric data, electrocardiograms, measurements of serum cholesterol, and dietary analyses. These investigators followed this study with a visit to Bologna, where they examined in much the same way 54 policemen. There were two reasons why these two cities were chosen; first, there was a great difference between the two places as to the diet of the populace, with particular reference to the fat content of the diet, and secondly, there was a most cordial support of the study by the medical scientists and government officials in both cities. In brief, it was found that the fat content of the diet and the serum cholesterol of the first three groups, that is, of the working men in Naples, was appreciably lower than that of either the members of the Neapolitan Rotary Club, the Bolognese policemen, or the Minnesota white-collar workers (205 in number) (Table IV, *A* and *B*), while other data, electrocardiographic, anthropometric, and the results of physical examination, were very much the same in all groups.

At the same time that these physiological, biochemical, and dietary analyses were going on, a few of us clinicians, Italian, Swedish, and American, visited the general hospitals in Naples, consulted the City Health Department, saw sick patients at home with the city physicians, and conferred with several professors of medicine of the University and with the leading cardiologist of southern

*Incidentally, it is of much interest that Clarence DeMar, who had run in more than 200 marathon races over an interval of many years, even after the age of 60 years, and who died of cancer at the age of 70, showed at autopsy capacious coronary arteries and a normal heart muscle.

Italy, Dr. A. Mattioli. Dr. Mattioli was at the time preparing a second edition of his book on myocardial infarction based on his personal experience in private practice with this disease which had affected many hundreds (over 2,000) of his well-to-do patients in Naples and in other places in southern Italy. These patients of his usually remained at home, because the facilities for such cases in the general hospitals were inadequate, and because there were very few private hospitals in Naples at that time for well-to-do medical patients. In contrast, we found that patients in the general population did not remain at home when they suffered from coronary thrombosis but availed themselves of the socialized medical wards in the large city hospitals.

TABLE IV

A. Physical Activity and Serum Cholesterol

	WORK CATEGORY	SAMPLE	MEAN SERUM CHOLESTEROL CONCENTRATION (MG. %)	
			AGE 25	AGE 50
Naples	Very heavy	Steel workers	131.0 ± 4.8	161.3 ± 3.4
	Moderate	Firemen	133.7 ± 3.8	180.3 ± 3.2
	Sedentary	Clerks	136.0 ± 8.9	173.3 ± 5.8
	Sedentary	Rotary Club		190
Bologna	Moderate	Policemen		210
Minnesota	Sedentary	White-collar workers		225

*B. Dietary Comparisons of Naples and Minnesota**

	NAPLES	MINNESOTA
Calories	3,010	2,980
Proteins (Gm.)	97	92
Proteins (per cent of all calories)	13	12
Total fats (Gm.)	65	140
Total fats (per cent of all calories)	20	42

The data for Italy and the United States are from the Food and Agriculture Organization's estimates for 1949, revised 1952, and from the United States Department of Agriculture, September, 1950. The data from Naples pertain to the fire department rations, supplemented by individual interviews in 1952. The data for Minnesota are from United States Food Consumption Surveys, and pertain to Minneapolis and St. Paul in the winter, spring, and fall of 1948. Note that the values for Naples are for the firemen (adults), while all others are per capita of total population.

In order to discover the prevalence of coronary thrombosis and myocardial infarction in the general population of Naples, we made ward rounds on a number of occasions in several city hospitals. For the practical purposes of later comparisons we concentrated on all patients in the open wards who were 40 to 70 years old, and we carefully checked by history, examination, and electrocardiogram those individuals who were thought to have coronary heart disease. Then we went to Bologna and did the same thing there.

In the spring of 1955, we repeated these studies in Sardinia, which has a somewhat isolated island population, and our findings closely resembled those of the year before in Naples, except that we found too few well-to-do inhabitants for any comparable comparison in that group.

TABLE V. TOTAL MEDICAL WARD MALE CASES AND MALE PATIENTS WITH CORONARY HEART DISEASE IN NAPLES, SARDINIA, BOLOGNA, LUND (SWEDEN), BOSTON, AND TWIN CITIES (U.S.A.). AGED 40 to 70 YEARS

LOCATION	MEDICAL WARD CASES	CORONARY CASES	PER CENT
Naples, Italy	239	7	2.9
Sardinia	76	4	5.2
Bologna, Italy	157	14	8.9
Lund, Sweden	91	12	13.1
Boston, U.S.A. (all racial origins)	166	30	18.0
Boston, U.S.A. (Italian origin)	212	39	18.3
Twin Cities, U.S.A.	234	61	26.0
Minneapolis, U.S.A. (Veterans Hospital)	150	45	30.0

TABLE VI, A.—MEAN TOTAL CONCENTRATION OF CHOLESTEROL (MG. PER 100 ML. OF SERUM) WITH AGE IN ITALIAN MEN STUDIED IN NAPLES* AND IN BOSTON

BOSTON						NAPLES					
AGE IN YEARS				CHOLESTEROL		AGE IN YEARS				CHOLESTEROL†	
NO.	RANGE	MEAN	S.D.	MEAN	S.D.	NO.	RANGE	MEAN	S.D.	MEAN	S.D.
71	20–34	29.1	3.5%	227.7	31.7%	40	20–34	27.9	—	175.4	32.4%
118	35–50	42.1	3.8%	246.6	43.5%	43	35–54	42.6	—	193.4	31.9%
189	20–50	37.2	7.3%	239.2	42.4%	83	20–54	35.5	8.9%	184.7	33.2%

*Data taken from Page 331, A.M.A. Arch. Int. Med., 93:328-336, 1954.
†Cholesterol values were corrected by a factor of 0.836 to account for difference in the cholesterol method then used, according to Clin. Chem., 1:34, 1955.

TABLE VI, B.—COMPARATIVE FOOD CONSUMPTION DATA

	ITALIAN NATIONAL*	NEAPOLITAN FIREMEN*	U. S. A.†	U. S. A. ITALIANS
Calories	2,340	3,010	3,220	3,450
Protein (Gm.)	75	97	97	120
Per cent Protein Calories	13	13	12	14
Fat (Gm.)	50	65	148	164
Per cent Fat Calories	19	20	41	43

*Data taken from A.M.A. Arch Int. Med., 93:328-336, 1954.
†Data compiled from *Consumption of Food in the United States, 1909-1952, Agriculture Handbook 62,* September, 1953, U. S. Department of Agriculture.

TABLE VII, A.—COMPARISON OF DIETARY INTAKE OF FAT AND THE SERUM CHOLESTEROL (BETA LIPOPROTEIN) CONTENT IN MINERS AND DOCTORS IN FUKUOKA, JAPAN, IN JAPANESE LABORERS IN HAWAII, AND IN JAPANESE WORKMEN IN CALIFORNIA[3]

SUBJECTS	FAT INTAKE (%)	SERUM CHOLESTEROL (MG. %)
Miners (Fukuoka)	12	106
Doctors (Fukuoka)	22	152
Laborers (Hawaii)	32	178
Workmen (California)	40	210

TABLE VII, B.—MEAN ALPHA AND BETA LIPOPROTEIN-CHOLESTEROL CONCENTRATIONS IN THE BLOOD SERUM OF SEDENTARY JAPANESE MEN, AGED 40 TO 49, MATCHED AS TO RELATIVE FATNESS: ALSO AVERAGE PERCENTAGE OF CALORIES PROVIDED BY FATS IN THE DIETS OF THESE SAME MEN[3]

PLACE	FAT CALORIES (%)	SERUM CHOLESTEROL (MG. %)	
Shime	13	40.3	120.3
Honolulu	32	40.4	183.0
Los Angeles	40	35.2	212.7

TABLE VIII, A.—SUMMARY OF HOSPITAL PATIENTS AND OF PATIENTS WITH CORONARY HEART DISEASE IN KYUSHU UNIVERSITY MEDICAL CLINICS, FUKUOKA, JAPAN, AND IN THE KUAKINI HOSPITAL, HONOLULU, HAWAII. (AGED 40 TO 70 YEARS)

	MEDICAL CASES			CORONARY CASES			
	M	F	TOTAL	M	F	TOTAL	%
Kyushu University (1955)	1,136	680	1,816	8 (0.7%)	3 (0.4%)	11	0.6
Kuakini Hospital (1955)	273	239	512	18 (6.6%)	7 (3.0%)	25	4.9

TABLE VIII, B.—EXPERIENCE WITH JAPANESE PATIENTS OF THREE PRIVATE CLINICS IN JAPAN, AND THREE IN HAWAII DURING THE MONTH OF MARCH, 1956*

PLACE	NUMBER OF PATIENTS SEEN		
	TOTAL	HYPERTENSIVE	CORONARY
Honolulu	433	50	34
Fukuoka	381	38	1

*Data collected by Dr. B. Bronte-Stewart and Dr. Paul D. White.

Finally, when I returned to Boston, I took the opportunity to check with my medical associates at home, and through the kindness of authorities at the Boston City Hospital, I had access to two groups of patients, one consisting of open-ward medical cases of all racial origins, aged 40 to 70 years, and the other of open-ward medical cases of first or second generation Italian males of the same age. Meanwhile, similar clinical series were analyzed in the Twin Cities (Minneapolis and St. Paul) in the U.S.A., and in the city of Lund in Sweden. The results of these analyses are shown in Table V. From the table it is evident that the populations of Bologna and Lund hold intermediate positions between the general populations of Naples and Sardinia and both the mixed and Italian populations in America.

We recognized, of course, as we have stated above, that other environmental factors besides fat in the diet may well play a role in the genesis of serious coronary atherosclerosis, and that heredity too must be a potent factor, but there seemed to be less difference in such factors between the ways of life of the average Neapolitan at home and those of the average American, whether or not of Italian ancestry, except in the amount of physical exercise. Such factors include, besides diet and exercise, emotional "stress and strain," use of tobacco and alcohol, local customs such as the use of "leisure" time, climate, and X (not yet identified). Much additional study of these other factors, as well as of diet and exercise, must be carried out in order to draw final conclusions.

Also in Boston, Dr. Stare, Dr. Trulson, expert in dietary studies, Dr. McCann, Dr. Miller, and I carried out a study of 200 healthy males whose parents had come from southern Italy (in the neighborhood of Naples) or who had been born there and had come to the U.S.A. as young children. This study included family, medical, and dietary histories, physical examinations, electrocardiograms, and determinations of serum cholesterol. Some of the results of this study are shown in Tables VI, A and VI, B, which also present comparable figures from the Neapolitan investigation already referred to.

In 1956, Dr. Keys and his wife, who is an expert biochemist and has helped greatly in his researches, Dr. Bronte-Stewart, of Cape Town, South Africa, and I, with the invaluable assistance of Professor Noboru Kimura and his associates of Kyushu University, Fukuoka, Japan, and Dr. Nils Paul Larsen, of Honolulu, Hawaii, made a study, like those in Italy, of three groups of Japanese: 424 Japanese living in southern Japan (in particular, comparing 156 coal miners with 54 physicians); 143 southern Japanese who had migrated 20 to 30 years earlier to work in Hawaii; and 45 Japanese (Nisei) living in California. Some of the results are summarized in Table VII, A and B. It is seen that the coal miners had less fat in their diet and less cholesterol in their blood than did the doctors in Japan, while the Japanese in Hawaii and California had more of each than did their former fellow citizens in Japan.

While we were in Japan, we made statistical analyses of coronary thrombosis in various cities there. Coronary thrombosis is more common in Tokyo and in Kyoto than farther south in Fukuoka, but it is everywhere much less common than in the U.S.A., although increasing steadily in prevalence (at least statistically). As we had done two years earlier in Naples, we consulted in Fukuoka

the professors of Kyushu University and visited their wards, and in Honolulu we made observations at the Kuakini Hospital, where many Japanese are taken care of. We found that the Japanese in the Kuakini Hospital had more coronary thrombosis and at younger ages than did the Japanese in Fukuoka. Of 1,136 men aged 40 to 70 in the medical wards of the Kyushu University Hospital, during the year 1955, only 8, or less than 1 per cent (0.7 per cent), had myocardial infarcts,* while among 273 Japanese men of the same age distribution in the Kuakini Hospital, during the year 1955, there were 18 cases of myocardial infarction, or 6.6 per cent. The average diet of the Japanese men in Fukuoka contained 1,994 calories, with 7 per cent thereof in fat (consisting almost entirely of vegetable oil); in Honolulu the diet was much richer in fat and included animal fat. Table VIII, A presents some of our findings. In Japan, we went also to a community hospital and a miners' hospital and visited the offices and clinics of several private practitioners in order to find out if there were any or many patients with coronary heart disease being taken care of outside the large general hospitals. We found that such cases were rare in the practice of any one physician (Table VIII, B). We did the same thing in Hawaii, where many more Japanese patients with coronary thrombosis were being seen in private practice than was the case in Japan.

Finally, in the fall of 1957, I again joined Ancel Keys and his group of physiological and biochemical investigators in studies of two groups of men aged 45 to 65 years, who comprised 96 to 97 per cent of the male population of that age group in two towns, Nicotera, on the edge of Calabria in the toe of Italy, and Castelli, in the middle of Crete (southeast of Herakleion), where in each case the chief industry was the manufacture of olive oil; very little animal fat was ingested in these locales. There was no malnutrition in either town, nor was there any appreciable obesity. Dietary studies revealed that the total fat content made up from 32 to 38 per cent of the total calories in Crete, and three fourths of this fat was in the form of olive oil. In the Nicotera area the diet was also quite high in olive oil, but the total fat content was somewhat less than that in Crete. Measurements of the serum cholesterol gave average figures of 180 mg. per cent for Nicotera, and 199 mg. for Crete, as compared with 165 mg. for Naples. Twelve-lead electrocardiograms of 598 men aged 45 to 65 years in Nicotera showed clear-cut evidence of myocardial infarction in only 4 (0.6 per cent). In Crete, electrocardiograms of 657 men aged 45 to 65 years showed clear-cut evidence of old myocardial infarction in only 2 (0.3 per cent). For comparison, in Framingham, Massachusetts, of 864 males aged 45 to 60 years, 6 (1 per cent) showed clear electrocardiographic evidence of myocardial infarction.

Also, several of us visited the hospitals in the vicinity of both Nicotera and Castelli and found extremely few cases of coronary heart disease in the wards. In both places I met with the physicians of the area and, except for one specialist in Herakleion, the doctors all emphasized the rarity of treating cases of coronary thrombosis or even of angina pectoris. The cardiologist in Herakleion (the chief center of the north coast of Crete, and about 35 miles from Castelli) reported

*Statistics through the courtesy of Professor Kimura.

to me the details of his recent experience with cardiac patients. Among 528 "cardiac" patients examined by him in 1956 and 1957, he found only 30 cases of myocardial infarction, while hypertensives numbered 281, rheumatics 168, cor pulmonale cases 39, congenital cardiacs 7, and syphilitic cardiacs 3. Thus, there was only a small number of cases of coronary thrombosis in the series (actually 6 per cent as compared with at least five times that number in Boston).

Thus, whatever other environmental factors or agents may play a major or a minor role in serious atherogenesis of the coronary arteries and probably also of the aorta and cerebral arteries and in the production of coronary thrombosis with or without myocardial infarction, it would appear from my personal experience in population studies during the last few years that, given the hereditary candidate or host for the disease, the diet, in particular the fat in the diet, is probably of considerable importance. It has also become obvious that the details of the diet, including the kind of fat, the total calories, and the protein content, requires much more intensive study. It does not yet appear that race itself is of great significance, but it is certain that sex is. The disease is not simply a matter of an aging process. The place of physical exercise, of work, of emotional stress and strain, of tobacco and alcohol, and of possible or probable X factors (not yet identified) must be thoroughly investigated in the years to come, both in experimental animals, especially in primates, and in man himself. Our recent success in enlisting a very high proportion of the members of certain ages of populations to volunteer for such studies is very encouraging, as is the wholehearted cooperation of international experts in physiology, biochemistry, nutrition, and cardiology working as teams in various parts of the world. Such pioneering in the field needs the full moral and material support of doctors and laymen alike all over the world in order to meet the present serious challenge to the life and health of the leaders in business, the professions, the arts, science, and government in all countries. I am optimistic about the future control of coronary heart disease, at least in youth and middle age, if our current research develops adequately.

REFERENCES

1. Gertler, M. M., and White, P. D., with the aid, advice, and assistance of Bland, E. F., Fertig, J., Garn, S. M., Lerman, J., Levine, S. A., Sprague, H. B., and Turner, N. C.: Coronary Heart Disease in Young Adults, A Multidisciplinary Study, Cambridge, Mass., 1954, Harvard University Press.
2. Pomeroy, W. C., and White, P. D.: J.A.M.A. **167**:711, 1958.
3. Keys, A., Kimura, N., Kusukawa, A., Bronte-Stewart, B., Larsen, N., and Keys, M. H.: Ann. Int. Med. **44**:83, 1958.

Transmembrane Electrical Potentials in Ventricular Tachycardia and Fibrillation

Charles E. Hogancamp, M.D., Milton Kardesch, M.D., William H. Danforth, M.D., and Richard J. Bing, M.D., St. Louis, Mo.

Excitation patterns during cardiac arrhythmias have been studied repeatedly by the use of the electrocardiogram and the surface electrogram. Since the advent of the micropuncture technique of Ling and Gerard,[1] it has been possible to extend this type of study to individual myocardial fibers. This paper will report observations on the electrical and mechanical events which follow the initiation of ventricular tachycardia and ventricular fibrillation in the guinea pig heart. In addition, an attempt will be made to relate electrical and mechanical activity in alternation of the heart.

MATERIALS AND METHODS

Guinea pigs were anesthetized with pentobarbital (100 mg./Kg.). The hearts were quickly removed and Stannius' ligatures were placed about the atrioventricular grooves. The hearts were then placed in a lucite chamber of 150-milliliter capacity surrounded by a thermostatically controlled water bath. They were bathed in Tyrode's solution constantly gassed by a mixture of 95 per cent oxygen and 5 per cent carbon dioxide passed through a gas disperser. This composition of gas imparted a pH of 7.4 to the bathing fluid. The bathing fluid temperature was kept constant at 38° C. Fig. 1 illustrates the experimental system.

Transmembrane resting and action potentials were recorded by a modification of the technique of Ling and Gerard.[1] Glass microelectrodes with tips of 0.5 to 1 micron in diameter were prepared by use of the instrument designed by Alexander and Nastuk.[2] The electrodes were filled with 3M KCl by boiling, followed by cooling in a vacuum chamber. Electrodes with resistances of 10 to 30 megohms were employed. A platinum wire was led from the interior of the electrode, by means of a short input grid lead, to an adjacent cathode follower tube (RCA 1620) with a small grid current (10^{-11} A). A micromanipulator supported both the electrode and the cathode follower to permit simultaneous movements. A chlorided silver wire connected to the ground served as the reference potential. Voltages were led from the cathode follower through a conventional D.C. amplifier to a DuMont 322A dual-beam cathode-ray oscillograph. Voltage calibrations were made by the use of an A.C. power supply system which produced peak-to-peak potential differences of the desired magnitude. The deflections were linear with voltages over the range of 10 to 100 millivolts.

From the Washington University Medical Service, Veterans Administration Hospital, St. Louis, Mo.

This work was supported by Veterans Administration Hospital, St. Louis, Mo., U.S. Public Health Service Grant No. H-2678, The Life Insurance Medical Research Fund, The American Heart Association, and the Tobacco Industry Research Fund.

Received for publication Sept. 12, 1958.

In the experiments utilizing only one microelectrode, one beam on the oscillograph served as a zero reference potential. When recordings were made by the use of two microelectrodes, prior base-line levels were photographed as they were superimposed on the gridded oscillographic screen. Contractions of the heart were recorded by the use of a small Statham strain gauge (No. 147) attached to the ventricular apex.

Electrical potentials were recorded from multiple superficial ventricular cells in each preparation. A sudden drop in potential evidenced entry into a fiber. Contraction of the heart was occasionally sufficiently vigorous to break the electrode tip or to dislodge it from the cell interior. This disadvantage was overcome with stabilization of a portion of the muscle by resting a wire loop lightly on the surface and performing the fiber penetrations within the enclosed area.

After preliminary observations and recordings of intracellular resting and action potentials and of ventricular contractions in the spontaneously beating or electrically driven ventricles, arrhythmias were produced by the application of a few crystals of aconitine to the heart surface.

Experiments were performed with a total of 60 hearts. Of these, 31 were studied with a single microelectrode alone. In 22 preparations mechanical contractions were recorded in addition to measurements of transmembrane potentials with one microelectrode. In 7 hearts two microelectrodes were employed.

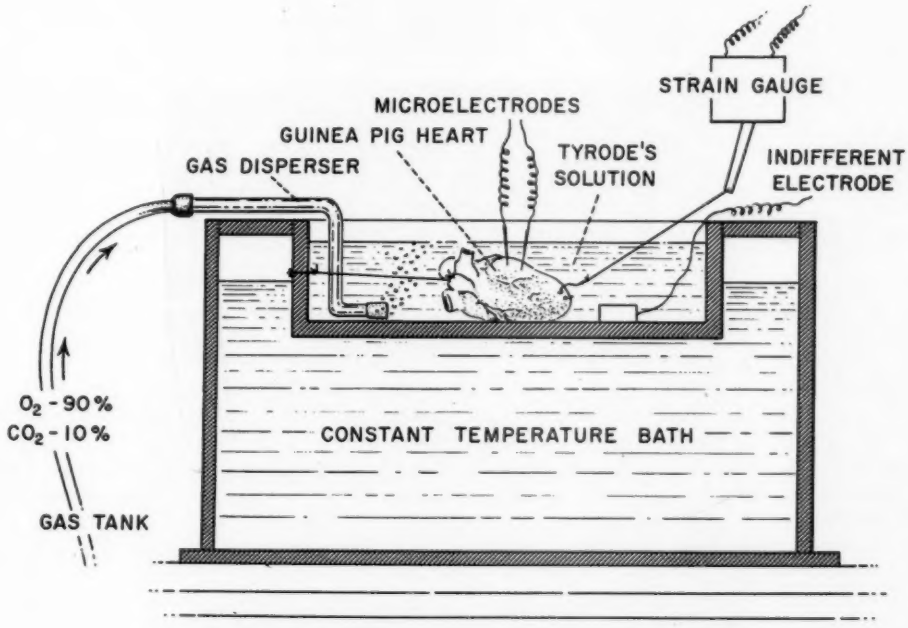


Fig. 1.—Schematic representation of the experimental system.

RESULTS

After the application of aconitine to the ventricle there was usually a latent period of from 2 to 7 minutes, followed by a period of ventricular tachycardia lasting from 3 to 10 minutes. At the time of transition from ventricular tachycardia to a disorganized rhythm, two to five mechanically asynchronous areas could be observed through a dissecting microscope. Within the following few minutes, more fractionation of mechanical activity became evident. However, the extreme tremulous incoordination seen in larger mammalian hearts with ventricular fibrillation was not assumed by the guinea pig ventricle.

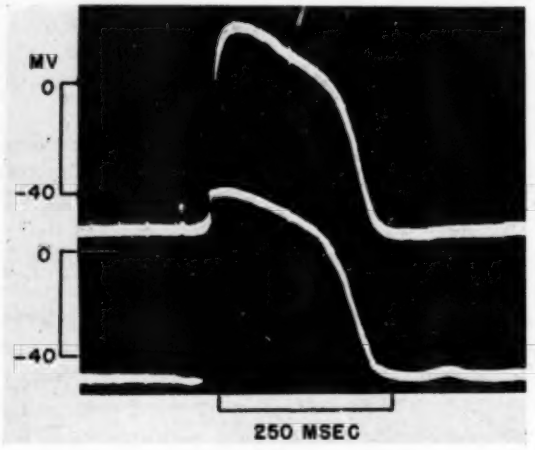


Fig. 2.—Simultaneous recording of action potentials from two ventricular fibers of an electrically stimulated guinea pig heart.

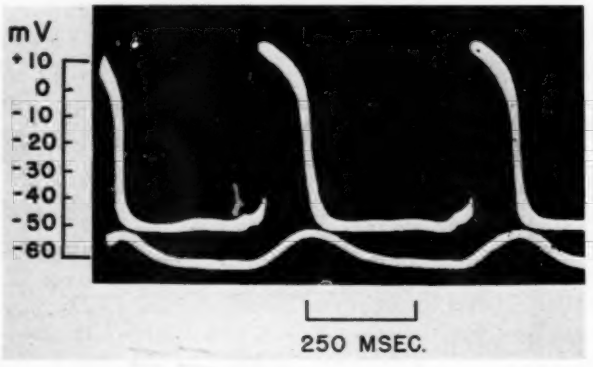


Fig. 3.—Intracellular action potentials from guinea pig ventricle electrically stimulated. The top illustration demonstrates action potentials of a single fiber. On the bottom is a mechanogram. The upstroke indicates ventricular contraction.

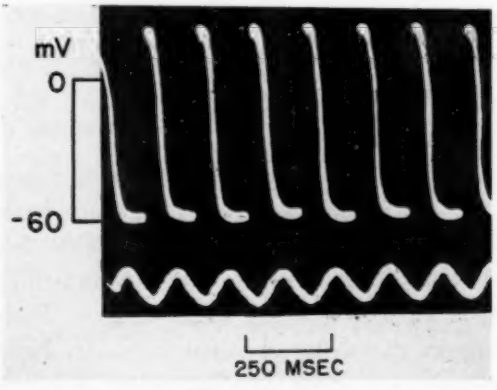


Fig. 4.—Ventricular tachycardia at a rate of 390 beats per minute. Action potentials and mechanogram.

Normal Membrane Resting and Action Potentials of Guinea Pig Ventricular Fibers.—Figs. 2 and 3 illustrate transmembrane potentials of fibers in the electrically stimulated ventricle. Noteworthy is the absence of an initial phase of rapid repolarization. A definite phase of slow repolarization (the plateau) is followed by a period of faster repolarization, during which reconstitution of the membrane resting potential occurs. The average value of the resting potential was found to be 57 millivolts. Overshoot values averaged 15 mv., resulting in an average action potential amplitude of 72 mv. This magnitude of resting potential is somewhat higher than that found by Johnson,[3] who reported a value of 52.8 mv.

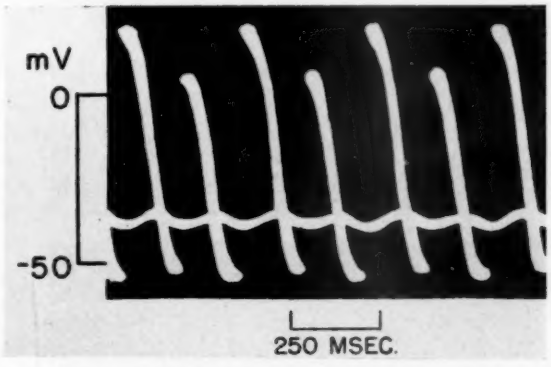


Fig. 5.—Prominent electrical alternation in a single ventricular fiber. Slight but definite mechanical alternation is present.

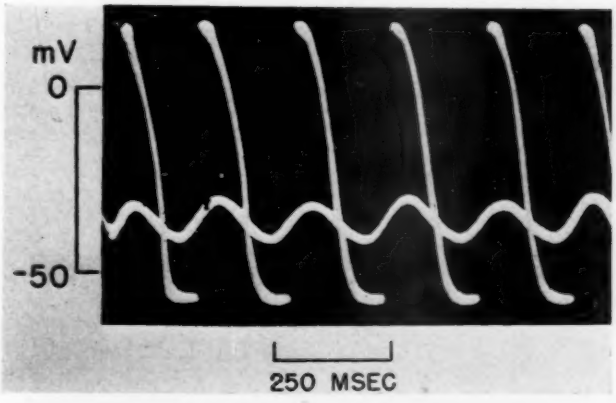


Fig. 6.—Mechanical alternation without an associated single fiber electrical alternation.

Membrane Potentials in Ventricular Tachycardia.—In 37 of the 60 hearts there was a recognizable period of ventricular tachycardia. This was evanescent in a few, lasting only 30 to 60 seconds; however, in most preparations this rhythm persisted 3 to 10 minutes prior to its transition into ventricular fibrillation. Heart rates in individual experiments ranged between 260 and 390 beats per minute. Fig. 4 demonstrates intracellular action potentials and a mechanogram

from a heart with an extremely fast rate (390 per minute). The action potential duration has shortened to 70 milliseconds from the original 200 milliseconds obtained during electrical stimulation.

Alternation in the height of action potentials was observed in 20 of 37 hearts which exhibited ventricular tachycardia. The amplitude of the alternating action potential varied from fiber to fiber, and in some cases the amplitude was insufficient to reach the zero reference potential. Electrical alternation was a very transitory phenomenon in this type of preparation and usually presaged the onset of ventricular fibrillation. Because of the short duration of alternation, exploration of multiple cells was accomplished as quickly as possible. In a se-

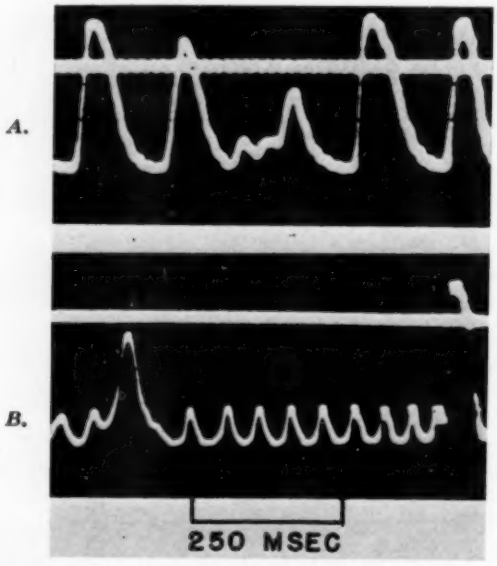


Fig. 7.—*A*, Action potentials at the beginning of ventricular fibrillation. The straight line represents the zero reference potential. *B*, Ventricular fibrillation. Small rapid oscillations at the rate of 900 per minute probably represent electrotonic currents from an adjacent focus of rapid impulse formation.

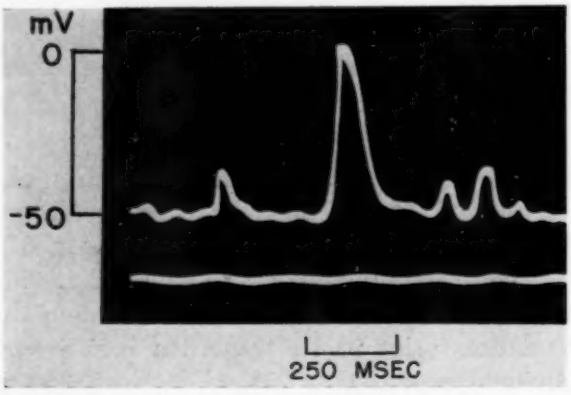


Fig. 8.—Membrane electrical potentials (top) and mechanogram (bottom) in ventricular fibrillation.

quence of fiber penetrations, electrical alternation could be recorded from one third to two thirds of the cells. In the remainder of the cells, however, regular action potentials were still present. Alternation of amplitude was the predominant change seen, although an accompanying change in the contour of the repolarization limb was frequently observed.

Alternation in the strength of ventricular contraction was seen several times, with and without electrical alternans (Figs. 5 and 6). Mechanical alternation and single fiber electrical alternation are both evident in Fig. 5. It is of interest that in the experiments employing both a microelectrode and a strain gauge, electrical alternans was never recorded in the absence of an associated mechanical alternans. The relationship appeared to be concordant in all cases; that is, the lesser action potential was associated with the weaker ventricular contraction.

Ventricular Fibrillation.—In 23 of the 60 preparations ventricular fibrillation was the initial arrhythmia. In the remainder it was preceded by ventricular tachycardia. In either case the recorded action potentials exhibited irregularity and incomplete depolarizations. Fig. 7,*A* illustrates action potentials recorded at the beginning of ventricular fibrillation. With the passage of time (5 to 15 minutes) and the fractionation of mechanical activity there could frequently

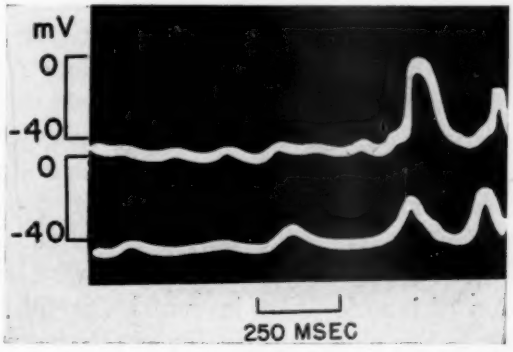


Fig. 9.—Ventricular fibrillation. Electrical activity recorded from two fibers in close proximity (less than 1 mm.).

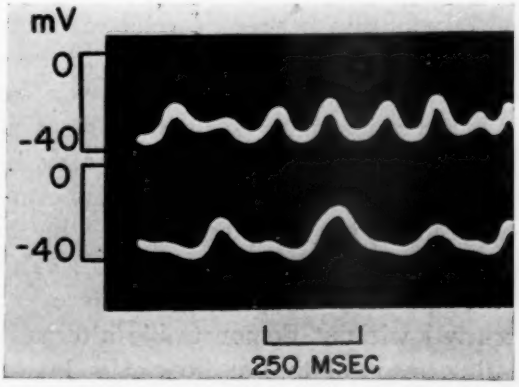


Fig. 10.—Ventricular fibrillation. Electrical activity recorded from two fibers 1 cm. apart.

be recorded very rapid oscillations of electrical activity with interspersed action potentials (Fig. 7,*B*). In Fig. 8, measurable mechanical activity has practically ceased and the action potentials are irregular and variable in amplitude and in duration. Figs. 9 and 10 represent simultaneous recordings by two microelectrodes. When fiber penetrations were performed a short distance apart, an element of synchronism of action potentials was found to exist. With increased distances between the microelectrodes, less and less synchronism was present.

DISCUSSION

The difficulty in causing ventricular fibrillation in small mammalian hearts is well recognized.[4] In our hands the use of aconitine served as the only uniformly successful method of inducing this arrhythmia in the guinea pig ventricle. It is recognized that aconitine-induced fibrillation may not be the same as its counterpart in clinical situations; however, it seems more likely that aconitine-induced ventricular irregularities differ little from those instituted by other means. In support of this assumption Sano and his co-workers[5] found no difference in transmembrane action potentials in ventricular fibrillation produced by either aconitine or electrical stimulation.

The observations reported in this paper indicate that when aconitine-induced ventricular fibrillation begins in the guinea pig heart, the action potentials are only slightly irregular, with little change in amplitude. A greater degree of irregularity and more action potentials of small amplitude ensue in a few minutes. The observation that some element of synchronism exists between action potentials and neighboring fibers is different from that in the dog ventricle as reported by Sano and associates,[5] who found, except in very early fibrillation, no similarity in configuration between action potentials from two variously distant points. Their findings, in contrast to results reported in this paper, supported the concept of total incoordination of muscle fibers in ventricular fibrillation. The reason for this difference may be the closer positioning of the two microelectrodes in the experiments reported here. When the points were less than 1 mm. apart, a degree of synchronism was present. On the other hand, the difference in experimental results might be explained by a species variation.

The presence of electrical alternans in individual myocardial fibers bears some comment. The relationship between mechanical and electrical alternans has never been clear. One frequently exists without the other.[6-8] In fact, a small pulse beat may be associated with a large R wave on the electrocardiogram.[7] Nonetheless, the two forms of alternans occur in similar situations. It has been thought that perhaps the reason for the divergence may be due to a recording method or device strategically situated to measure one event only.

In the experiments reported in the present paper, mechanical alternans was always present when electrical alternans was recorded. The weaker contraction was associated with the smaller action potential. However, mechanical alternation occasionally occurred without demonstrable alternans in the single fiber electrode. It is tempting to speculate that alternation in action potentials would have been present had it been possible to record a sufficient number of myocardial

fibers. In view of the fact that, in general, changes in the state of the contractile elements do not appear to influence the height of the membrane action potential,[4,9] it seems more likely that changes in the action potential were primary and changes in mechanical contraction were secondary, than that the reverse was true.

There is no a priori reason for assuming that alternation has the same underlying mechanism in each situation in which it occurs. It is found with different clinical situations: congestive heart failure associated with a diseased myocardium, tachycardias, either atrial or ventricular, and for a few cycles following an extrasystole or dropped beat. Alternans in the last two situations does not carry the same grave prognosis as it does in the diseased heart.[10] The possible difference in underlying mechanism must be kept in mind when considering experimental data.

Kleinfeld and his associates[11] produced alternation of the action potential in the frog heart by the use of triiodothyronine. They were able to produce four distinct types of alternation: (1) alternation in the rate of depolarization, (2) alternation of repolarization, (3) alternation in the magnitude of the membrane action potential, and (4) alternation of hyperpolarization. These patterns of alternation apparently were not dependent on rate. Alternation in the electrocardiogram paralleled changes in the membrane action potential. Hoffman and Suckling,[12] using the microelectrode technique, found regular alternation in the shape of the repolarization curve at very rapid rates in the dog papillary muscle, but no changes in the height of the membrane action potential. Only at very rapid rates did small decreases in magnitude of the membrane resting potential and of the height of the action potential take place. These authors did not feel that the decrease in resting or action potentials occurred because of a cycle length so short that depolarization occurred before repolarization had been completed. Changes in the rate of repolarization of every other beat also occurred for several cycles following an extrasystole.

The present study shows alternation in the action potential occurring with marked tachycardia during the prefibrillatory stage. In contrast to the findings of Hoffman and Suckling,[12] the height of depolarization as well as the rate of repolarization changed. Also in contrast to the findings of these authors, depolarization of the smaller action potential frequently seemed to occur before repolarization of the larger had terminated (Fig. 5). If this is indeed the case, the diminished action potential and less forceful contractions were not surprising, because the membrane was still in the relative refractory stage.

Alternation in the height and configuration of the action potential was not observed in all cells of any preparation studied but was present in only one third to two thirds of the cells punctured in any single heart. Fibers showing alternation were not grouped but were scattered widely throughout the ventricle. Each fiber from which electrical events were recorded showed action potentials with every beat. Therefore it is unlikely that some myocardial cells take part in every second beat only and are refractory during the alternate cycle, a concept which has been widely held in various forms since 1882.[13-16] Rather, in this preparation electrical and mechanical alternation appeared to be related to behavior of individual fiber membranes and contractile elements.

SUMMARY

Ventricular tachycardia and fibrillation have been induced in the intact ventricle of the guinea pig by the use of aconitine. The micropuncture technique was used to record single fiber electrical activity.

Ventricular fibrillation was characterized by irregular action potentials of varying amplitude. Simultaneous recording of electrical activity from two fibers on the ventricular surface revealed partial synchronism of action potentials when the fibers were in close proximity. The synchronism was not evident when the explored fibers were at a distance. The disorganization of guinea pig ventricular fibers during fibrillation was not total.

Single fiber electrical alternans was frequently observed during ventricular tachycardia and was associated with mechanical alternans. Mechanical alternans was seen occasionally without demonstrable single fiber electrical alternans. It is suggested that in this circumstance the appropriate fibers were not selected for microelectrode penetration, since it was found that all cells did not participate in electrical alternation in any one preparation. It would appear, therefore, that alternation of the heart, both electrical and mechanical, may be related to alternate variations in behavior of individual fiber membrane and contractile elements.

REFERENCES

1. Ling, G., and Gerard, R. W.: J. Cell. & Comp. Physiol. **34**:383, 1949.
2. Alexander, J. T., and Nastuk, W. L.: Rev. Sci. Instr. **24**:529, 1953.
3. Johnson, E. A.: J. Pharmacol. & Exper. Therap. **117**:237, 1956.
4. Brooks, C. M., Hoffman, B. F., Suckling, E. E., and Orias, D.: Excitability of the Heart, New York, 1955, Grune & Stratton, Inc.
5. Sano, T., Tsuchihashi, H., and Shimamoto, T.: Circulation Res. **6**:41, 1958.
6. Windle, J. D.: Quart. J. Med. **4**:435, 1910-11.
7. Lewis, T.: On the Mechanism and Graphic Registration of the Heart Beat, Ed. 3, London, 1925, Shaw & Sons, Ltd., pp. 434-447.
8. Hamburger, W. W., Katz, L. N., and Saphir, O.: J.A.M.A. **106**:902, 1936.
9. Trautwein, W., and Dudel, J.: Pflügers Archiv. ges. Physiol. **260**:24, 1954.
10. Levine, S. A.: Clinical Heart Disease, Ed. 4, Philadelphia, 1951, W. B. Saunders Co.
11. Kleinfeld, M., Stein, E., and Magin, J.: Am. J. Physiol. **187**:139, 1956.
12. Hoffman, B. F., and Suckling, E. E.: Am. J. Physiol. **179**:123, 1954.
13. Gaskell, W. H.: Philosophical Transaction of the Royal Society **173**:993, 1882.
14. Hering, H. E.: Ztschr. f. exper. Path. u. Therap. **12**:325, 1913.
15. Mines, G. R.: J. Physiol. **46**:349, 1913.
16. Brody, J. G., and Rossman, P. L.: J.A.M.A. **108**:799, 1937.

A Phonocardiographic Study of the Apical Diastolic Murmurs in Pure Mitral Insufficiency

Theodore F. Hubbard, M.D., F. Lowell Dunn, M.D., and D. D. Neis, M.D.
Omaha, Neb.

This study was undertaken to examine systematically the phonocardiographic characteristics of the apical diastolic murmurs and sounds observed in a group of patients with pure mitral insufficiency. An attempt is made to characterize the auscultatory and phonocardiographic features of these murmurs which differentiate them from the murmurs of organic mitral stenosis, and by correlation with other physiologic events in the cardiac cycle to present evidence concerning their mode of production.

MATERIALS AND METHODS

This study was based upon phonocardiographic and other physiologic studies of 18 patients with isolated high-grade pure mitral insufficiency who were selected for having auscultatory or phonocardiographic apical diastolic murmurs. In addition to the usual clinical studies the degree of mitral insufficiency was assessed either by the dye-dilution method of Korner and Shillingford[1] or by our own modification of this technique.[2] The volume of regurgitation in this group of patients ranged from 40 to 80 per cent of the left ventricular output. The absence of organic mitral stenosis was established in 10 of the patients by direct left atrial and ventricular pressure measurements obtained either by left heart catheterization or at the time of mitral valve surgery. The absence of mitral stenosis was indicated by the absence of an atrioventricular pressure gradient during diastasis. A small gradient often developed during the peak of rapid ventricular filling, and in the patients with the highest grades of mitral insufficiency the ventricular pressure would often show a steep rise and "overshoot" the atrial pressure or exhibit a few oscillations about the atrial pressure wave at the termination of rapid filling. A small atrioventricular gradient frequently developed during atrial contraction in the patients who had sinus mechanisms. The remaining 8 patients were considered to have no mitral stenosis on the basis of the finding of mitral orifices of at least 4 cm. in greatest diameter at the time of surgical exploration or at autopsy. Patients with other associated valvular lesions were excluded. Sixteen patients had atrial fibrillation at the time of study; 2 had sinus mechanisms with first and second degree atrioventricular block.

All patients had one or more phonocardiographic studies with a Sanborn Twin-Beam phonocardiograph, recording from the apex and at at least one other position on the precordium. The

---

From the University of Nebraska College of Medicine, and the Bishop Clarkson Memorial Hospital, Omaha, Neb.
Supported in part by grants from The United States Public Health Service and the Nebraska Heart Association.
Received for publication Sept. 23, 1958.

phonocardiograms were recorded with both bell and diaphragm and with stethoscopic and logarithmic amplification at paper speeds of 75 mm. per second. The phonocardiograms were recorded simultaneously with the electrocardiogram and piezoelectric apex cardiogram, and these were used for synchronization with recordings of left heart pressure. A more detailed study of the murmurs of a number of the patients was made by means of a specially constructed phonocardiographic amplifier with a continuously variable selective band-pass filter. These phonocardiograms were recorded oscillographically at a paper speed of 200 mm. per second.

Although there is no general agreement concerning the graphic definition of a heart sound as opposed to a murmur, for our purposes a diastolic sound was characterized as having dominant frequencies in the range of 15 to 75 cycles per second, and major oscillations lasting for less than 0.10 second.

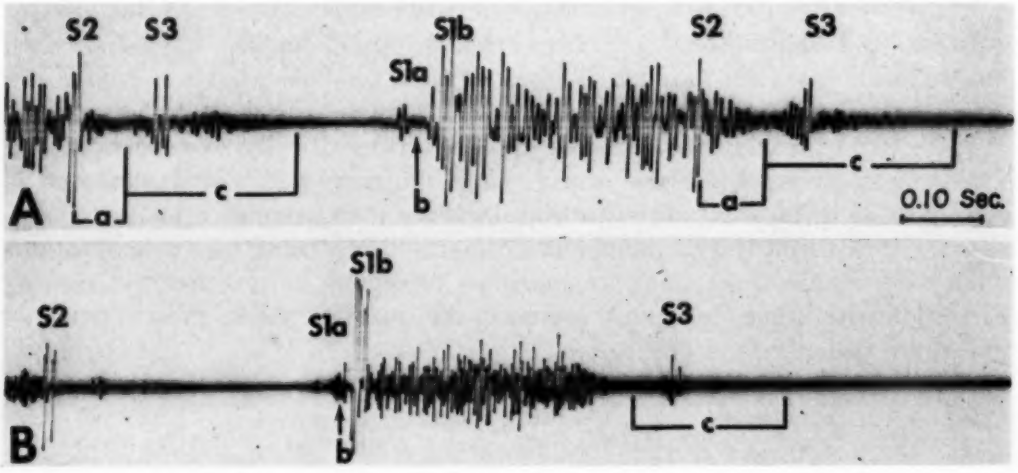


Fig. 1.—Phonocardiograms recorded at the apex of a patient with severe mitral insufficiency. *A*, Recorded with filter at 200 cycles/sec. *B*, Recorded at 400 cycles/sec. In this case the regurgitant murmur has its onset between the muscular and valvular components of the first sound and its termination after the second sound at the time of mitral opening and onset of the diastolic murmur. *S1a:* First (muscular) component of first heart sound. *S1b:* Valvular components of first heart sound. *S2:* Second heart sound. *S3:* Third heart sound. *a:* Component of regurgitant murmur between aortic valve closure and mitral opening. *b:* Component of regurgitant murmur between onset of contraction of left ventricle and mitral closure. *c:* Early mid-diastolic murmur.

THE MURMUR AND SOUNDS

In 12 of the patients the high-frequency systolic murmur of mitral insufficiency persisted from 0.03 to 0.10 second after the major components of the aortic second sound. This was best demonstrated by phonocardiograms utilizing a band-pass filter of from 200 to 400 cycles per second and recording at 200 mm. per second. With this type of recording it was often possible to demonstrate a short component of the mitral regurgitant murmur between the muscular and valvular components of the first heart sound (Figs. 1 and 2,*D*).

The most consistent and characteristic diastolic murmur was a short mid-diastolic murmur with its major components corresponding in time to the rapid-filling phase of ventricular diastole (Fig. 2). It was of maximal intensity about the apex and had dominant frequencies in the range of 75 to 150 cycles per second. This murmur was present in all but one of the patients. In 12 of the patients

the murmur had its onset at the time of opening of the mitral valve, or shortly thereafter, reaching its maximum intensity at or shortly after the third sound and diminishing in intensity to a termination shortly after the end of rapid ventricular filling. The intensity pattern of the murmur when recorded at the appropriate frequency usually corresponded to a small atrioventricular pressure gradient developing during rapid filling (Fig. 3). Only with very short diastolic cycles would the murmur last throughout diastole. In one patient the rapid-filling murmur occurred as described above but without the development of an atrioventricular gradient during rapid filling. In 2 patients the murmur started with or just after the third sound. In both of these patients, tracings were recorded only with the Sanborn instrument.

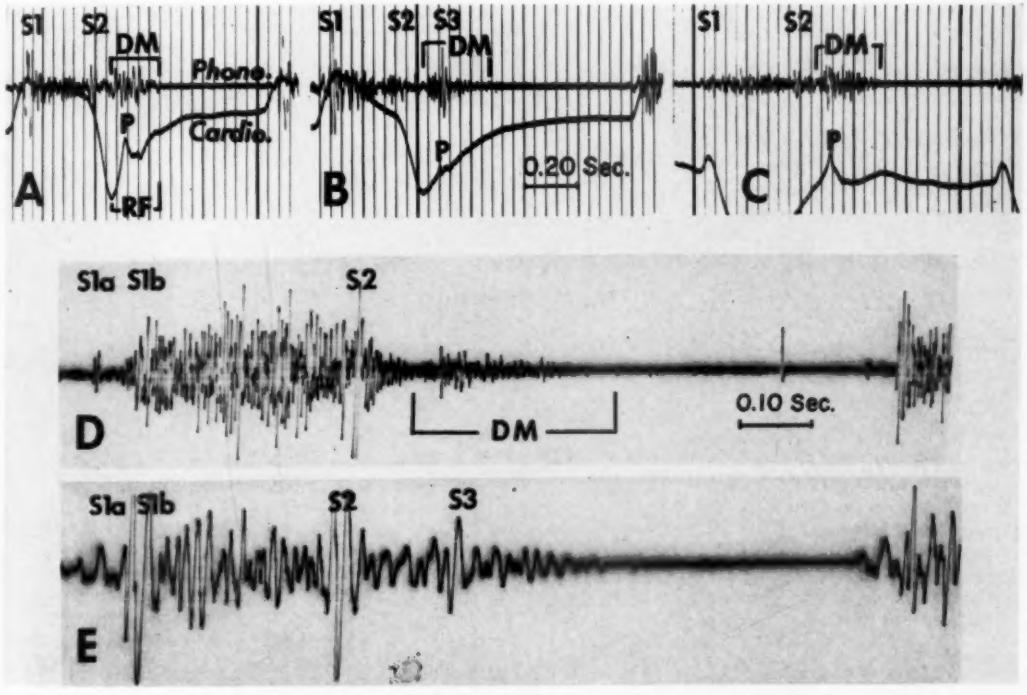


Fig. 2.—Phonocardiograms and piezoelectric cardiograms recorded from the apex in four patients with severe mitral insufficiency, showing the configurations of the diastolic murmurs. *A*, Record from a patient with severe mitral insufficiency, utilizing the Sanborn phonocardiograph with microphone bell and logarithmic amplifier. *B*, Record from a patient with severe mitral insufficiency, utilizing microphone bell and logarithmic amplifier. *C*, Record from a patient with severe mitral insufficiency with a palpable early diastolic thrust just medial to the apex, obtained with diaphragm microphone and logarithmic amplifier. *D* and *E*, Apex phonocardiograms obtained, respectively, with filters at 200-2,000 cycles/sec. and 50-2,000 cycles/sec., from a patient with severe mitral insufficiency. *DM:* Diastolic murmur. *RF:* Rapid-filling phase of apex cardiogram. *P:* Peak of rapid-filling wave in apex cardiogram.

In 3 of the patients with the highest grades of mitral insufficiency it was possible on recording the phonocardiogram at 200 to 300 cycles per second with fast paper speed to separate the above-mentioned murmur into two or more components corresponding to the instantaneous atrioventricular pressure gradients occurring during rapid ventricular filling (Fig. 4). The first component

starts with the opening of the mitral valve, reaches a peak at about the trough of the ventricular pressure wave (point of maximal A-V pressure gradient), and diminishes rapidly with the rapid rise in ventricular pressure. When the ventricular pressure overshoots and rises transiently above the atrial pressure, a second short component of the murmur is inscribed. Finally, the ventricular pressure falls slightly below the atrial pressure for a brief period, and a soft final component of the murmur is inscribed. These findings suggest a transient period of diastolic ventriculo-atrial flow as the mechanism of the aforementioned second component, perhaps associated with closure of the valve as noted below.

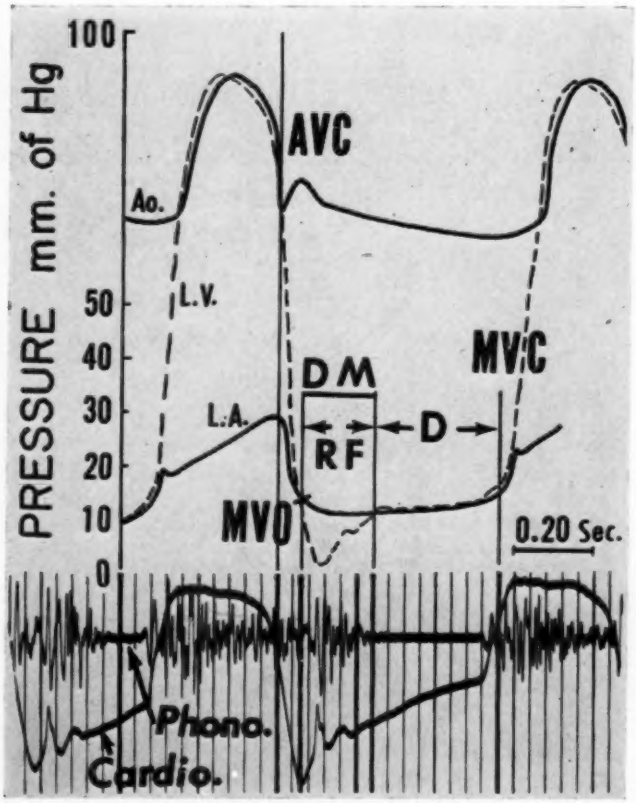


Fig. 3.—The relationship of the apical heart sounds to the events in the cardiac cycle in a patient with severe mitral insufficiency. The left atrial, left ventricular, and aortic pressures have been redrawn to simultaneous coordinates. The phonocardiogram is recorded logarithmically with microphone bell. ***Ao:*** **Aortic pressure.** ***L.V.:*** **Left ventricular pressure.** ***L.A.:*** **Left atrial pressure.** ***AVC:*** **Aortic valve closure.** ***MVO:*** **Mitral valve opening.** ***MVC:*** **Mitral valve closure.** ***DM:*** **Diastolic murmur.** ***RF:*** **Rapid-filling phase of ventricular diastole.** ***D:*** **Diastasis.**

In some of the other patients some of the cycles showed transient interruption or a decrease in intensity of the murmur just after the third sound, possibly due to a similar mechanism (Fig. 1,*A*). In 2 patients with sinus rhythm and first degree atrioventricular block, an atrial presystolic murmur started with the onset of atrial contraction and lasted until just before the first sound (Fig. 5).

A third heart sound could be delineated in the stethoscopic or low-frequency

recording in 14 of the patients. This corresponded in timing to the trough of the ventricular pressure wave in early diastole and the peak of the rapid-filling wave of the apex cardiogram. In 4 of the patients a forceful, palpable impulse corresponding to the third heart sound was present at or just within the apex. In 2 patients with prolongation of atrioventricular conduction, prominent atrial gallop sounds were present in late diastole, associated with presystolic murmurs. In the one of these patients who had had left heart catheterization the sound corresponded to the peak of the left atrial *a* wave. In 4 patients an additional sound occurred 0.05 to 0.07 second after the third heart sound, and was usually recorded with greatest amplitude medial to the apex or along the left sternal border (Fig. 6). In the 2 of these patients in whom left heart pressure measure-

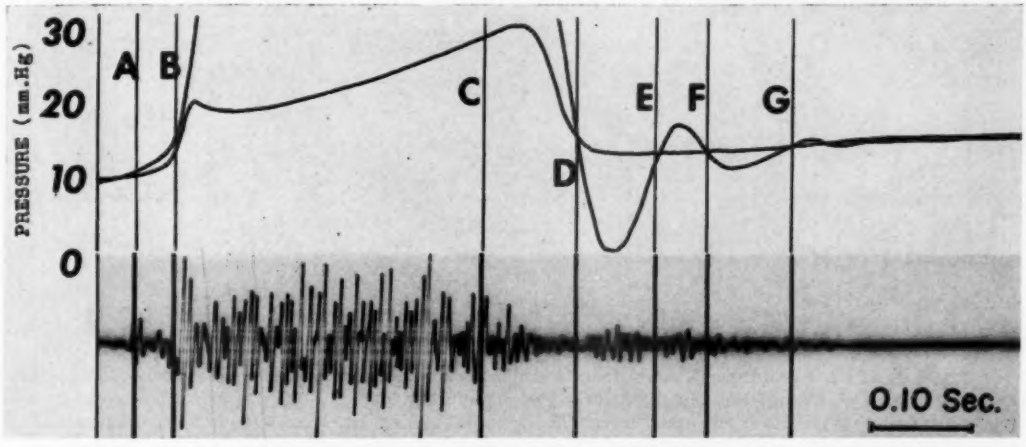


Fig. 4.—Left heart pressures and apex phonocardiogram from a patient with severe mitral insufficiency; portions of the left atrial and ventricular pressures have been redrawn to simultaneous coordinates with the phonocardiogram. The phonocardiogram was recorded at 200 cycles/sec. *A*, Muscular component of first sound with onset of ventricular contraction. *B*, Valvular component of first sound with mitral closure. *C*, Aortic second sound. *D*, Regurgitant murmur ends and diastolic murmur begins at mitral opening. *E*, Onset of second component of diastolic murmur as atrial pressure rises above the ventricular pressure. *F*, Onset of third phase of diastolic murmur. *G*, End of rapid filling near termination of murmur.

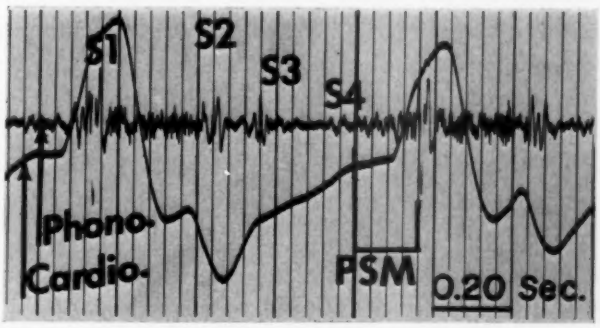


Fig. 5.—Phonocardiogram and apex cardiogram from a patient with pure mitral insufficiency and prolonged A-V conduction. The phonocardiogram is recorded logarithmically with microphone bell. The tracing shows a third heart sound, an atrial sound (*S4*), and a presystolic murmur.

ments were made this sound corresponded to the peak of the left ventricular pressure rise following the major dip in rapid filling as the ventricular pressure rose transiently above the atrial pressure. The murmur was usually interrupted at the time of this sound. An opening-snap sound could not be detected in any of these patients by auscultation, but a faint opening snap could be recorded in 4 patients.

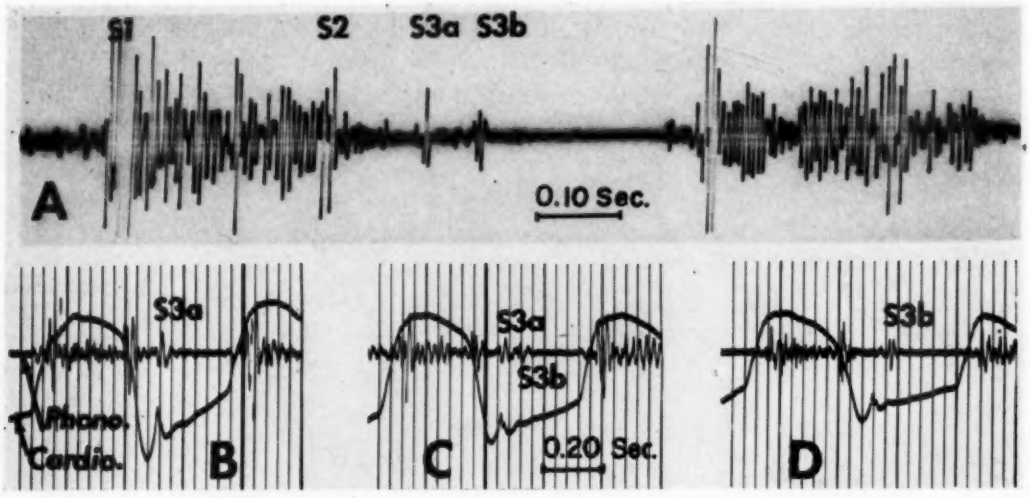


Fig. 6.—*A*, Apex phonocardiogram from a patient with mitral insufficiency recorded at 200 cycles/sec. *B*, *C*, and *D*, Phonocardiograms from a patient with mitral insufficiency recorded, respectively, from the apex, just medial to the apex, and at the lower left sternal margin. The phonocardiograms show a diastolic sound (*S3b*) shortly after the third sound which is tentatively attributed to transient mitral closure. This sound is best recorded toward the left sternal border.

DISCUSSION

The diastolic sounds and murmurs described above correlate well with the apparent dynamics of atrioventricular filling in high-grade mitral insufficiency. In such a group of patients the very high atrioventricular flow rates during the phase of rapid filling would appear to be a major factor in the production of the short early mid-diastolic apical murmur. Since normal individuals during strenuous exercise may have atrioventricular flows as high as some of those reported here without the development of diastolic murmurs, the factor of dilatation of the left atrium and left ventricle is probably equally important in the production of this murmur. Turbulence will occur at lower flow rates as the abruptness of taper of the channel to or from the atrioventricular orifice increases. In this study, 13 of the patients had roentgenologically estimated left atrial volumes in excess of 800 c.c.

A component of this murmur was often due to the low-frequency vibrations of the third heart sound usually attributed to vibrations of the ventricular wall with its sudden distention early in rapid filling.[3] The occurrence of this sound at or just before the onset of the rapid pressure rise in the left ventricle is compatible with this idea. Another low-frequency component occurring about 0.04

second after the third sound was observed in a few patients, and is tentatively ascribed to transient mitral valve closure occurring as the ventricular pressure rose transiently above the atrial. The latter phenomenon was also apparently responsible for occasional dimunition or interruption of the murmur during rapid filling, and perhaps for a short period of diastolic regurgitation. In the presence of very high-grade mitral insufficiency this steep rise and "overshoot" of the ventricular pressure is probably due to elastic recoil of the ventricular wall following its sudden distention by the large volume of atrioventricular flow.

In the presence of prolonged A-V conduction a fourth sound and presystolic murmur occurred, with the development of an atrioventricular pressure gradient during atrial contraction. The development of turbulence during this period

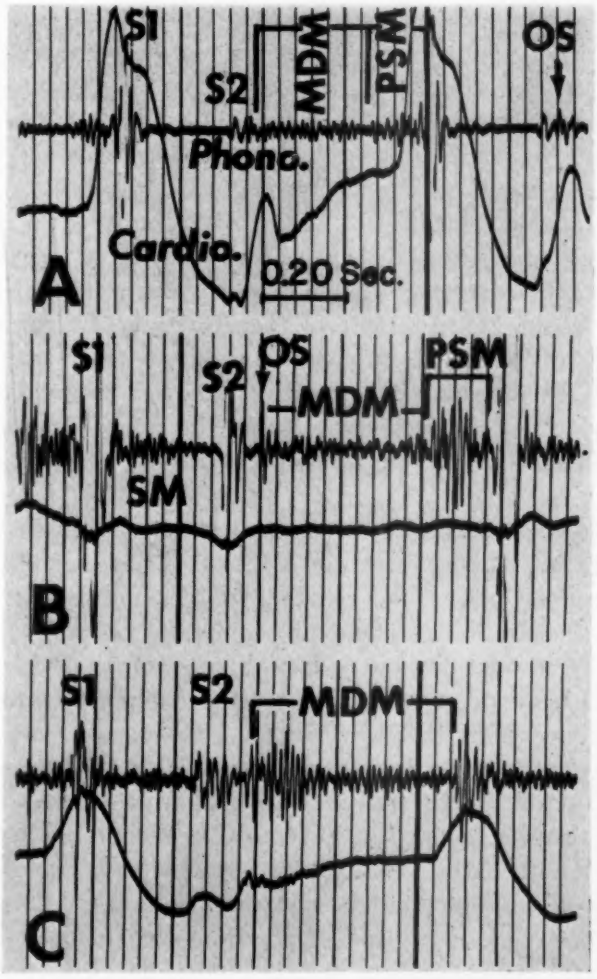


Fig. 7.—*A*, Apex phonocardiogram from a patient with pure mitral stenosis. *B*, Apex phonocardiogram from a patient with mitral stenosis and dynamically insignificant mitral insufficiency. *C*, Apex phonocardiogram from a patient with mitral stenosis and significant mitral insufficiency. The phonocardiograms were recorded logarithmically with microphone bell. In the patient with significant mitral insufficiency the diastolic murmur shows increased intensity during the phase of rapid filling.

is again probably related to dilatation of the left heart chambers, because such functional presystolic murmurs have been described in other circumstances associated with dilatation of the left heart chambers.[4]

When recorded at appropriate frequencies the higher frequency systolic murmur of mitral regurgitation usually extended, with decreasing intensity, beyond the time of closure of the semilunar valves to the onset of the rapid-filling murmur with mitral opening. This was coincident with the decreasing ventriculo-atrial gradient through isometric relaxation.

Other circumstances associated with high left atrioventricular flow rates and varying degrees of dilatation of the left atrium and ventricle may be associated with murmurs of "relative" mitral stenosis, notably ventricular or aortic left-to-right shunts and active rheumatic myocarditis. Dilatation of the left heart chambers associated with coronary artery and hypertensive heart disease less commonly produces such murmurs.

Luisada and others[4] have described certain features of the murmur of relative mitral stenosis which differentiate it from the murmur of organic mitral stenosis. The findings in this group of patients are similar with a few exceptions. In organic mitral stenosis there is usually after the second sound a silent interval of from 0.06 to 0.11 second, at which time the mitral opening-snap sound occurs. The murmur has its onset with this sound or a few hundredths of a second thereafter; there is then very gradual decrescendo until atrial contraction or mitral closure. If the stenosis is extremely mild or the diastolic period very long, the murmur may fade out before either of these events. Occasionally, the earlier vibrations may be of increased amplitude and simulate or actually be due to a third heart sound. When the latter occurs, it indicates minimal stenosis or significant associated valvular insufficiency. When the valve is rigid and inflexible, the opening-snap sound may disappear or be too soft to be detected by auscultation.

In relative stenosis due to severe mitral insufficiency the systolic murmur of mitral regurgitation usually continues with rapid decrescendo to or just before opening of the mitral valve. An opening-snap sound is not audible but can be recorded occasionally. Mitral opening generally occurs later than in mitral stenosis, but there is considerable variation in timing of this event in mitral insufficiency. With mitral opening the murmur increases rapidly to a peak of intensity at or shortly after the third sound. By auscultation the separation of the third sound from the murmur, or vice versa, may be difficult. The murmur then diminishes rapidly and terminates at about the time of the end of rapid filling, its total duration being from 0.16 to 0.24 second. Except in very short diastolic cycles or with early atrial contraction the murmur will disappear well before the sound of subsequent atrial contraction or the first sound.

In the presence of sinus rhythm, mitral stenosis is usually associated with a presystolic murmur corresponding to an increasing atrioventricular pressure gradient during atrial contraction. This may occur also with pure mitral insufficiency with sinus rhythm, particularly if atrioventricular conduction is prolonged or if the diastolic interval is quite short. The other familiar characteristics of the heart sounds in organic mitral stenosis, such as prolongation of the

Q-M_1 interval, the variability of this delay according to previous diastolic cycle length, and the snapping quality of M_1, are not observed with relative mitral stenosis. When a significant degree of mitral insufficiency is associated with organic mitral stenosis, there is usually a prominent increase in the intensity of the diastolic murmur corresponding to the period of rapid ventricular filling. This phenomenon may be useful in assessing the dynamic importance of the associated murmurs of mitral insufficiency in the presence of organic mitral stenosis (Fig. 7).

SUMMARY

A phonocardiographic study was made of the apical diastolic murmurs and sounds encountered in a group of 18 patients with high-grade pure mitral insufficiency. The characteristic diastolic murmur occupied early mid-diastole and usually corresponded to a small atrioventricular pressure gradient developing during rapid ventricular filling. A protodiastolic third heart sound was usually present. In the presence of sinus rhythm with prolongation of atrioventricular conduction a presystolic gallop sound and presystolic murmur could be detected. In a few patients an additional low-frequency sound in rapid filling and a component of the diastolic murmur were thought to be due, respectively, to transient valve closure and diastolic mitral regurgitation. Some observations were made concerning the initial and terminal portions of the systolic murmur of mitral regurgitation.

REFERENCES

1. Korner, P. I., and Shillingford, J. P.: Clin. Sc. **14**:553, 1955.
2. Hubbard, T. F.: J. Lab. & Clin. Med. **51**:835, 1958.
3. Kuo, P. T., Schnabel, T. G., Blakemore, W. S., and Whereat, A. F.: J. Clin. Invest. **36**:1035, 1957.
4. Luisada, A. A., Haring, O. M., and Zilli, A. B.: Ann. Int. Med. **42**:644, 1955.
5. Luisada, A. A.: Recent Advances in the Diagnosis of Rheumatic Heart Disease **17**:781, 1954.

The Passivity of the Pulmonary Vasculature in Hypoxia

Simon Rodbard, M.D., Ph.D., and Michiyoshi Harasawa, M.D., D.Med. Sc. Buffalo, N.Y.*

The mode of regulation of the pulmonary circulation has recently become the subject of intensive investigation. Some workers have held that pulmonary vessels, like the vessels of the systemic circulation, are capable of active vasoconstriction in response to hormonal, neurogenic, or even mechanical stimuli.[1-6] Others, noting the weak muscular development in the pulmonary arteries of various animals, including man, and the delayed pressure response to drugs, have questioned the significance of pulmonary vasomotion and have suggested that blood flow through the lungs takes place passively, being determined by the difference in the pumping action of the two ventricles.[7,8] Another concept has held that variable compression of the alveolar capillaries by intrapulmonary air pressure assists in the regulation of the pulmonary blood flow.[9]

The vasoactive concept was supported by the report, in 1946, of von Euler and Liljestrand[10] that in the cat, hypoxia produced an elevation of the mean pulmonary arterial pressure. This effect was not influenced by vagotomy or by extirpation of the stellate ganglia, suggesting that it was due to a local action of anoxia on the pulmonary vessels. These striking results were soon confirmed and extended.[11-15] Others found that hypoxia in rabbits[16,17] or dogs[18,29] caused a rise in pulmonary arterial pressure; furthermore, it was reported that the cardiac output measured by the Fick principle remained unchanged or was decreased during the hypoxic episode. Similar data were reported for man.[30-34] Some workers who used the Fick method[35-37] could not confirm these results. The overwhelming conclusions drawn, however, were that the pulmonary vascular resistance had increased as a result of hypoxia.

Quantitative evaluation of vascular resistance must be based on simultaneous measurements of the blood flow and pressure. In most of the above-mentioned studies the pulmonary blood flow was determined by the Fick prin-

---

From the University of Buffalo Chronic Disease Research Institute, Buffalo, N. Y. (The University of Buffalo Chronic Disease Research Institute is supported in part by the New York State Department of Health.)

This study was aided by Grant H-2271 (C3) from the National Heart Institute of the United States Public Health Service.

Received for publication Oct. 1, 1958.

*Respirator and Rehabilitation Center Exchange Fellow of Dr. Okinaka's Clinic, University of Tokyo School of Medicine, Tokyo, Japan. The Center is aided by a grant from the National Foundation.

ciple. This method requires a "steady state" for at least the period of minutes necessary for the measurement of oxygen consumption. However, in acute, challenging conditions such as hypoxia, the possibility exists that readjustment and adaptation of the physiologic state may introduce serious errors into the Fick measurement.

In the present investigation the effect of hypoxia on pulmonary vascular resistance has been studied, taking care to measure the moment-to-moment flow through the lungs, simultaneously with direct measurements of the systolic, mean, and diastolic pressures in both the pulmonary and the systemic arterial systems. The results challenge the concept that hypoxia produces pulmonary vasoconstriction.

EXPERIMENTAL METHOD

Observations were made in 15 dogs weighing 9 to 22 kilograms. Anesthesia was induced by intravenous pentobarbital sodium (30 mg./Kg.). After tracheotomy a single-lumen catheter was inserted into the trachea; in 10 animals Dale and Rahn's double-lumen catheter[38] was introduced into one main bronchus in order to separate the ventilation of the two lungs. The lungs were ventilated with adjustable positive pressure, using the pneophore.* The thorax was opened and the fourth rib was removed to facilitate placement of the cannulas. Connective tissue surrounding the pulmonary arteries was cleared away, taking care to avoid sectioning of large nerve strands.

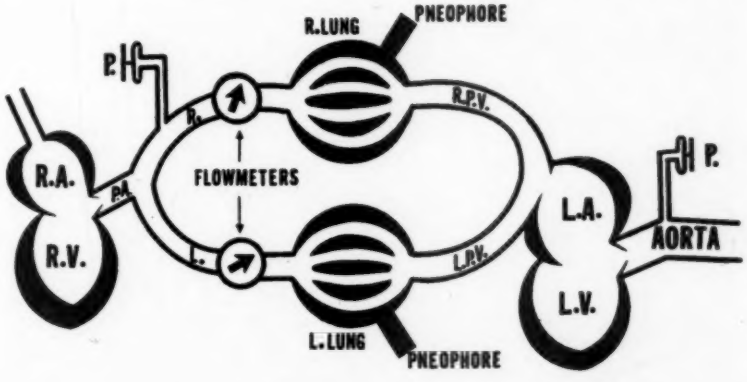


Fig. 1.—Scheme of method for direct measurement of pulmonary blood flow. Blood from the right atrium (*RA*) passed through the right ventricle (*RV*) to the pulmonary artery (*PA*) and thence through a flowmeter in each of the right (*R*) and left (*L*) branches to the intrapulmonary vessels. In some experiments each lung was ventilated separately via pneophore. The blood then passed through the right and left pulmonary veins (*RPV* and *LPV*) and the left atrium (*LA*) and ventricle (*LV*) to the aorta and systemic circulation. Pressures (*P*) were recorded by manometers.

The cannulas of a rotameter were inserted into the two ends of the left main pulmonary artery (Fig. 1). Similar cannulation of the right pulmonary artery was then carried out. As a result of these interventions the blood flow through each lung could be recorded continuously in relatively intact animals. The sum of the instantaneous flows through the two flowmeters gave the total pulmonary blood flow, equal to the cardiac output.

The lungs were ventilated at a rate of 16 to 25 per minute with positive pressure, using 95 per cent oxygen and 5 per cent carbon dioxide during the control periods. Hypoxia and anoxia were produced by giving 10 per cent oxygen in nitrogen, or by giving pure nitrogen. The air insufflation pressure and the respiratory rate were maintained unchanged in each experiment.

*Pneophore obtained from Mine Safety Appliance Co., Pittsburgh, Pa.

Heart rates and the pressures in the pulmonary and the carotid arteries were recorded continuously, using a Sanborn electromanometer and recorder. The oxygen and carbon-dioxide contents were measured by the method of Van Slyke and Neill on blood samples drawn at intervals from the carotid artery.

RESULTS

1. *Basal Conditions.*—After completion of the preparation and cannulation the systemic arterial pressures averaged 95/56 mm. Hg and ranged from 120/70 to 60/40; the pulmonary arterial pressure averaged 36/19 mm. Hg and ranged from 68/26 to 16/3, with a mean of 38/5. The right pulmonary blood flow averaged 0.73 L./min., ranging from 1.20 to 0.52 L., while the left pulmonary flow averaged 0.53 L./min., ranging from 0.96 to 0.22 L. During inspiratory insufflation of the lungs the entire pulmonary arterial pressure tracing was seen to be elevated 2 to 3 mm. Hg, and this was accompanied by a momentary slight reduction in flow through the lungs. No significant differences were observed in insufflation with air, pure oxygen, or 95 per cent oxygen with 5 per cent carbon dioxide.

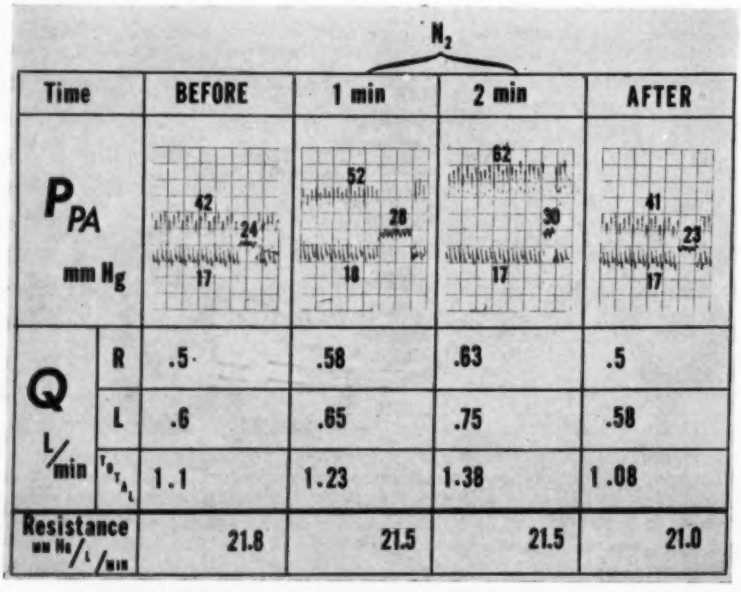


Fig. 2.—Cuttings from a representative experiment. The pulmonary arterial pressure (P_{PA}) in mm. Hg is shown before, during, and after the induction of pure nitrogen breathing. The number above the pressure tracing is the systolic value, while that below the tracing is the diastolic value, and the number over the damped portion of the trace is the electronically integrated mean pressure. The diastolic pressure is unchanged although the systolic and mean pressures rise during the episode of hypoxia. The blood flow (Q) through each lung is given in liters per minute. The calculated resistance, given in the lowest horizontal spaces, shows no change.

2. *Hypoxia.*—

a. *Nitrogen breathing:* Pure nitrogen was administered 15 times to both lungs in 10 experimental animals. In 10 trials on 5 animals, nitrogen was given for 1 to 2 minutes, followed by a return to the oxygen breathing. A typical

response is given in Fig. 2. At the end of 1 minute of nitrogen breathing, the oxygen content of the systemic arterial blood had decreased from 20 to 4 volumes per cent. In all cases the pulmonary systolic pressure increased progressively by 10 to 20 mm. Hg above the control values. The electronically integrated mean pulmonary pressure increased slightly with the increase in the systolic pressure. However, the pulmonary diastolic pressure remained almost unchanged during the experiment. The systemic systolic and diastolic pressures increased progressively in all cases for the first few minutes of anoxia. These changes in pulmonary and systemic blood pressures were accompanied in every case by increases in pulmonary blood flow of 5 to 15 per cent. The onsets of the rises and the times of the peaks were almost simultaneous for pressure and for flow.

Within 2 or 3 minutes after reinstitution of oxygen breathing, all pressures and flows returned to control levels. The heart rate decreased slightly during the anoxia test and returned to control values within a few minutes.

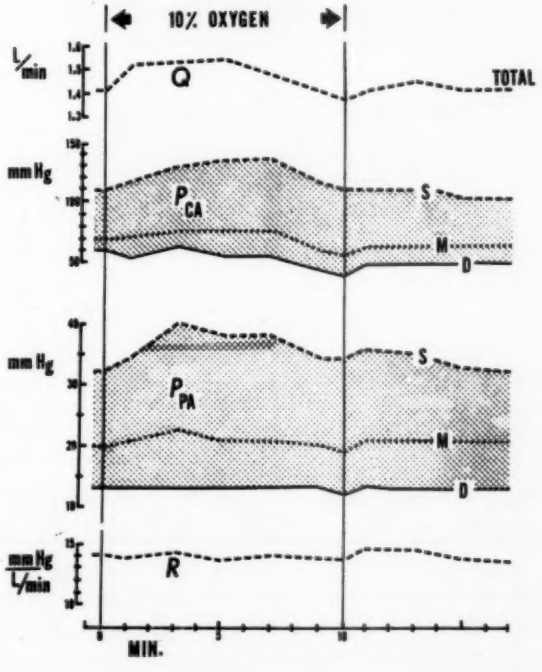


Fig. 3.—Effect of breathing 10 per cent oxygen, noted between the heavy arrows and the two vertical lines. The total flow (Q) is given in liters per minute. Pressures in the carotid artery (P_{CA}) are given as systolic (S), mean (M), and diastolic (D) in mm. Hg. Similar conventions are used for the pulmonary arterial pressures (P_{PA}). The calculated resistances as mm. Hg/liter/minute are given as R. Although the pressures increased during the first few minutes of hypoxia, the pulmonary vascular resistance was unaffected.

b. *10 per cent oxygen:* A gas mixture consisting of 10 per cent oxygen and 90 per cent nitrogen was tested for periods of 5 to 10 minutes 10 times in 7 experimental animals. Rises in pressures and flows similar to those noted above were observed, but these were less marked than those obtained with pure nitrogen (Fig. 3). The pulmonary blood flow and systolic pressure increased slightly,

but the diastolic pressure remained relatively unchanged. Within a few minutes after return to oxygen or air breathing, all changes had returned to the control levels.

3. *Unilateral Nitrogen or 10 Per Cent Oxygen.*—The possibility had to be considered that unilateral pulmonary hypoxia might show a vasoconstrictor effect, since under these circumstances the relative resistance to flow through the two lungs might become more evident in a redistribution of blood flow. Pure

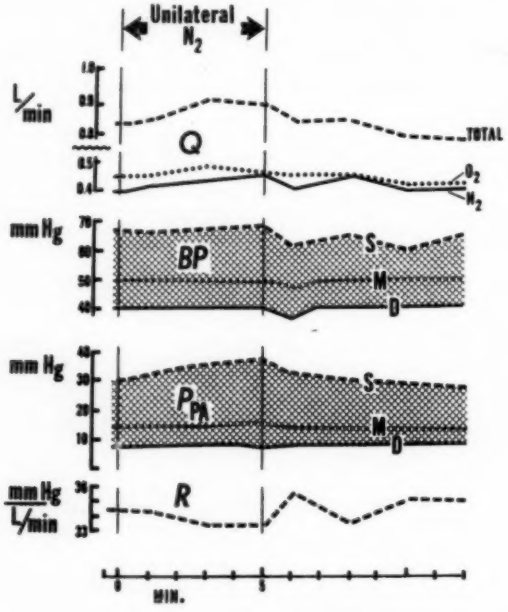


Fig. 4.—Effect of unilateral breathing of nitrogen. Conventions as in Fig. 3. *BP* is carotid arterial pressure. The flow through the lung which was insufflated with nitrogen is noted as a solid line (N_2); the flow through the lung receiving pure oxygen is given as a dotted line (O_2). Discussed in text.

	GAS	DURATION MIN.	EXPTS.	B. P.	BLOOD FLOW	RESIST.
BILATERAL	10% O_2	5 - 10	10	↗	↗	0
	N_2	1 - 4	15	↗	↗	0 - ↘
UNILATERAL	10% O_2	10	5	0	0 - ↗	0 - ↘
	N_2	5 - 10	10	0 - ↗	0 - ↗	0 - ↘

Fig. 5.—Summary table of data. Arrows show the changes observed. In this table B. P., blood flow, and resistance represent the changes in the pulmonary system.

nitrogen gas or a gas mixture containing 10 per cent oxygen and 90 per cent nitrogen was administered to one lung 15 times in 10 experimental animals for periods of 5 to 10 minutes, while the other lung was ventilated with 95 per cent oxygen and 5 per cent carbon dioxide. Changes in pressures and flows occurred, but

these were not as marked as those noted above (Fig. 4). The administration of either of the hypoxic gas mixtures to one lung was followed within 1 to 2 minutes by very slight increases in pulmonary blood flow through both the anoxic and the oxygenated lung. The pulmonary diastolic pressure remained unchanged or decreased slightly. The heart rate slowed slightly.

Within 2 or 3 minutes after a return to breathing 95 per cent oxygen with 5 per cent carbon dioxide the flows and pressures had returned to control values, and sometimes the resistance showed slight but probably insignificant and inconsistent increases during this period.

DISCUSSION

The measurement of resistance to flow through the pulmonary vessels is fraught with difficulty. Prior to the development of the techniques of cardiac catheterization, only limited information could be obtained concerning the physiologic modifications in pressure and flow in the pulmonary vessels. The recent extensive explorations of the vessels of the thorax with catheter, needle, and dye, have provided considerable data concerning the hemodynamics of the lesser circulation. However, the necessary limitations in the available indirect methods for the measurement of the pulmonary blood flow have prevented clarification of the problem of the responsiveness to stimuli of the pulmonary vascular bed.

Misinterpretation of the role of the pulmonary vessels can result from reliance solely on the pulmonary arterial pressure. This hazard is particularly notable when only mean pressures are recorded by mercury manometer, since this value is markedly affected by the systolic pressure, which in turn may reflect only an increase in stroke output. Both the systolic and the mean pressures can rise significantly, as our results show, without a change in the diastolic level. It can be stated that a rise in diastolic level during a steady state of flow may represent an increase in vascular resistance.

The very low end-diastolic arterial pressure of the normal pulmonary circuit approximates the pressure in the left atrium. At this time the flow is minimal. The sharp upstroke and rapid fall-off of the pulmonary arterial tracing suggests that a major portion of the blood flow through the lungs is completed during ventricular systole and early diastole, and that there is a significant part of the cardiac cycle when little or no flow takes place. This would suggest that a mean pressure value may introduce errors into the estimation of the vascular resistance.

The occurrence of a rise in venous return, and thus in cardiac output, would tend to raise the pulmonary arterial pressure even if the vascular bed remained unaffected by the induction of anoxia.

The problem of vascular resistance in the pulmonary circuit is further complicated by the fact that at the normal low pressures of this system most of the flow through the lungs occurs during right ventricular systole and early diastole. During the latter part of diastole the pulmonary arterial pressure may be nearly at ambient levels, and little flow through the pulmonary capillaries takes place. It is apparent that calculations of resistance under these circumstances may lead to error, since these must presume a continuous action of the resistance

throughout the cardiac cycle. Obviously, if the flow is taking place only part of the time, the resistance cannot be accurately gauged. In fact, the increased flow which sometimes takes place can occur during periods when the vascular bed is not in "use," and calculations may even suggest a reduction in resistance, as can be seen in Fig. 4. Certain facets of this problem are discussed in a separate communication.

It is well established that within 30 seconds after the onset of breathing oxygen-poor mixtures the cardiac output increases as a result of the development of a generalized systemic peripheral vasodilatation.[39-41] Such an effect is seen in Figs. 2, 3, and 5. This effect must necessarily reduce confidence in the measurement of flow by methods which require a steady state. Thus, the significant increase in pulmonary blood flow shown in the present study indicates that the apparent pulmonary arteriolar vasoconstriction may actually represent only an increased blood flow, without response by the pulmonary vasculature.

Similar results and analyses were obtained from the data when one lung was insufflated with nitrogen while the other was insufflated with a mixture of 95 per cent oxygen and 5 per cent carbon dioxide. Under these circumstances, no significant deviations in the distribution of flow through the two lungs occurred, despite the fact that even slight changes in pulmonary vascular resistance might have been expected to shunt significant volumes of the blood to the opposite lung. Fishman and associates[34] obtained essentially similar results in man. Our results suggest that unilateral anoxia has only a very small effect in increasing the cardiac output and pulmonary blood flow, presumably because the vasodilatation ordinarily resulting from severe hypoxia is not induced, since the systemic arterial blood has an adequate oxygen content.

Presumptive reductions in pulmonary vasomotor tone have been reported after the administration of adrenaline, and hypotensive and sympathoplegic drugs, especially in the treatment of hypertension.[42,43] These effects have been generally less striking than those reported in anoxia. Since all these agents also act on the systemic circulation, the possibility exists that the pulmonary effects are only secondary. It would appear that the question of the responsiveness of the pulmonary vessels to such vasoactive drugs requires reassessment.

If the evidence for active vasomotion in the pulmonary vessels is seriously challenged, the possibilities remain either that these important vessels have no active means of regulation, or that some other means, perhaps via the airways,[9] may operate to regulate the pulmonary blood flow.

In any event, the present results provide no support for the concept that the pulmonary blood vessels can respond to hypoxia or anoxia. Further studies to elucidate the mechanisms of regulation of the pulmonary blood flow and pressure are indicated.

SUMMARY

The blood flow through each of the main pulmonary arteries was measured by rotameter in the pentobarbitalized thoracotomized dog.

Induction of hypoxia by unilateral or bilateral insufflation of nitrogen or 10 per cent oxygen produced increases in pulmonary systolic and mean arterial

pressures, but the diastolic pressure was unaffected. The cardiac output was increased in every instance. The calculated pulmonary vascular resistance was unchanged. These data challenge the concept that hypoxia produces pulmonary vasoconstriction. Instead, the pulmonary vasculature appears to be passive under these circumstances.

We wish to acknowledge the excellent technical assistance of Francis Williams, M.A., and Daniel Fabricy, B.A.

REFERENCES

1. Edwards, W. S.: Am. J. Physiol. **167**:756, 1951.
2. Gorlin, R., Clare, F. B., and Zuska, J. J.: Brit. Heart J. **20**:346, 1958.
3. Daley, R.: Brit. M. J. **2**:173 and 249, 1957.
4. Fritts, H. W., Jr., Harris, P., Clauss, R. H., Odell, J. E., and Cournand, A.: J. Clin. Invest. **37**:99, 1958.
5. Yu, P. N., Nye, R. E., Jr., Lovejoy, F. W., Jr., Schreiner, B. F., and Yim, B. J. B.: J. Clin. Invest. **37**:194, 1958.
6. Ferri, F., Rovati, V., Panesi, M., Romanelli, R., and Righini, E.: Acta cardiol. **12**:269, 1957.
7. Hamilton, W. F., Woodbury, R. A., and Vogt, E.: Am. J. Physiol. **125**:130, 1939.
8. Lanari-Zubiaur, F. J., and Hamilton, W. F.: Circulation Res. **6**:289, 1958.
9. Rodbard, S.: Am. J. Med. **15**:356, 1953.
10. von Euler, U. S., and Liljestrand, G.: Acta physiol. scandinav. **12**:301, 1946.
11. Logaras, G.: Acta physiol. scandinav. **14**:120, 1947.
12. Nisell, O. I.: Acta physiol. scandinav. **16**:121, 1949.
13. Nisell, O. I.: Acta physiol. scandinav. **21**:Suppl. 73, 1950.
14. Nisell, O. I.: Acta physiol. scandinav. **23**:85, 1951.
15. Duke, H. N.: Quart. J. Exper. Physiol. **36**:75, 1951.
16. Dirken, M. N. J., and Heemstra, H.: Quart. J. Exper. Physiol. **34**:193, 1948.
17. Dirken, M. N. J., and Heemstra, H.: Quart. J. Exper. Physiol. **34**:213, 1948.
18. Atwell, R. J., Hickam, J. B., Pryor, W. W., and Page, E. B.: Am. J. Physiol **166**:37, 1951.
19. Peters, R. M., and Roos, A.: Am. J. Physiol. **171**:250, 1952.
20. Lewis, B. M., and Gorlin, R.: Am. J. Physiol. **170**:574, 1952.
21. Hall, P. W.: Circulation Res. **1**:238, 1953.
22. Hurlimann, A., and Wiggers, C. J.: Circulation Res. **1**:230, 1953.
23. Stroud, R. C., and Rahn, H.: Am. J. Physiol. **172**:211, 1953.
24. Rahn, H., and Bahnson, H. T.: J. Appl. Physiol. **6**:105, 1953.
25. Stroud, R. C., and Conn, H. L., Jr.: Am. J. Physiol. **179**:119, 1954.
26. Aviado, D. M., Jr., Ling, J. S., and Schmidt, C. F.: Am. J. Physiol. **189**:253, 1957.
27. Duke, H. N.: J. Physiol. **135**:45, 1957.
28. Borst, H. G., Whittenberger, J. L., Berglund, E., McGregor, M.: Am. J. Physiol. **191**:446, 1957.
29. Rivera-Estrada, C., Saltzman, P. W., Singer, D., and Katz, L. N.: Circulation Res. **6**:10, 1958.
30. Motley, H. L., Cournand, A., Werkö, L., Himmelstein, A., and Dresdale, D.: Am. J. Physiol. **150**:315, 1947.
31. Westcott, R. N., Fowler, N. O., Scott, R. C., Hauenstein, V. D., and McGuire, J.: J. Clin. Invest. **30**:957, 1951.
32. Doyle, J. T., Wilson, J. S., and Warren, J. V.: Circulation **5**:263, 1952.
33. Siebens, A. A., Smith, R. E., and Storey, C. F.: Am. J. Physiol. **180**:428, 1955.
34. Fishman, A. P., Himmelstein, A., Fritts, H. W., Jr., and Cournand, A.: J. Clin. Invest. **34**:637, 1955.
35. Aviado, D. M., Jr., Cerletti, A., Alanis, J., Bulle, P. H., and Schmidt, C. F.: Am. J. Physiol. **169**:460, 1952.
36. Nahas, G. G., Visscher, M. B., Mather, G. W., Haddy, F. J., and Warner, H. R.: J. Appl. Physiol. **6**:467, 1954.
37. Nahas, G. G., Mather, G. W., Wargo, J. D. M., and Adams, W. L.: Am. J. Physiol. **177**:13, 1954.
38. Dale, W. A., and Rahn, H.: J. Thoracic Surg. **29**:453, 1955.
39. Feldman, M., Jr., Rodbard, S., and Katz, L. N.: Am. J. Physiol. **154**:391, 1948.
40. Surtshin, A., Rodbard, S., and Katz, L. N.: Am. J. Physiol. **152**:623, 1948.
41. Rodbard, S., and Katz, L. N.: Circulation **12**:448, 1955.
42. Sarnoff, S. J., Berglund, E., and Sarnoff, L. C.: J. Appl. Physiol. **5**:367, 1953.
43. Sancetta, S. M.: Am. Heart J. **49**:501, 1955.

Determinations of Serum Enzymes in Surgical Patients: Value in Diagnosis of Complicating Myocardial Infarction

Raymond L. Weisberg, M.D., and John J. Sampson, M.D., San Francisco, Calif.

The exhibition of characteristic time curves of certain serum enzyme activities, especially of serum glutamic oxalacetic transaminase (SGO-T) and serum lactic dehydrogenase (SLDH), have proved valuable aids in the diagnosis of myocardial infarction in doubtful cases.[1-5] Doubt of the diagnosis arises frequently (1) when the diagnostic electrocardiographic changes are minimal, as with T-wave inversions only, or are obscured by bundle branch block or other pre-existing abnormalities; (2) when a history of prolonged characteristic cardiac pain is not obtained because (a) the pain is of short duration, (b) signs and symptoms other than pain are exhibited, such as faintness, hemiplegia, or pulmonary edema, or (c) the patient is incapable of expressing pain, as with certain psychoses or suppression of sensory responses by drug analgesia or anesthesia.

The latter type of pain suppression is important because myocardial infarction is not an infrequent occurrence in anesthetized patients during surgical procedures or in the immediate postoperative period, especially following hypotensive episodes. Approximately only one fourth of such cases present a history of characteristic pain at any time.[6] An index of suspicion of such a complication should be cultivated when the patient is elderly or has a history of prior coronary disease and demonstrates unexplained postoperative hypotension, tachycardia, or congestive heart failure. Electrocardiograms should be obtained in such cases but may not be clearly diagnostic. Such supporting evidence of myocardial infarction as fever, leukocytosis, and rapid erythrocyte sedimentation rate are often valueless following surgery.

Characteristic curves of increased activity of SGO-T and SLDH should assist in the diagnosis, but many investigations have been published (experimental[7-10]; clinical[11,12]) indicating that elevated SGO-T and SLDH activity is the expected result of either experimental or clinical surgical procedures because of (1) damage to the liver by the anesthetic agents or (2) trauma to skeletal muscle and other tissues. An exception to such statements is the report by Lawrence and Schulkins[13] of only a modest rise of SGO-T (32 to 40 units [U.]/ml.) in 5 of 12 operations involving thoracotomy and pulmonary resection. In 6 laparotomy procedures, there was only one (a cholecystectomy) in which there

From the Department of Medicine and the Harold Brunn Institute for Cardiovascular Research, Mount Zion Hospital and Medical Center, San Francisco, Calif.

Received for publication Oct. 15, 1958.

was an abnormal rise of the SGO-T activity (49 U./ml.) in this postoperative period.

Trauma (including infarction) of tissues other than the myocardium, liver, or pancreas will cause marked elevation of SGO-T and SLDH only when the tissue damage is extensive.[15-17] Acute damage to the liver by the anesthetic agents most frequently used in human surgery has not occurred in our personal experience.

It is the purpose of this paper to present a series of surgical cases which indicates that in the absence of preoperative hepatic damage, elevated SGO-T and SLDH levels in significant curves were not obtained in the postoperative period unless myocardial infarction occurred.

METHODS

SGO-T, SLDH, and serum glutamic peruvic transaminase (SGP-T) determinations were made simultaneously by the modified techniques of Karmen, Wroblewski and LaDue, and Wroblewski and Cabaud.[18-21] Normal ranges for this laboratory were 1 to 32 U./ml. for SGO-T and SGP-T, and 100 to 250 U./ml. for SLDH. Twenty-one surgical cases operated, 19 under general anesthesia, were studied. There were 13 laparotomies, 2 thoracotomies, and 6 other types of operation. In general, determinations of serum enzymes were made (1) preoperatively and (2) postoperatively between 6 and 20 hours, between 24 and 48 hours, and between 48 and 70 hours. SGO-T assays were made in all cases, SLDH in 19 cases, and SGP-T in 13 cases. In 10 cases, indices of hepatic damage were obtained by the Bromsulphalein (BSP) one-hour retention test and by measurement of SGP-T, which rarely rises above 50 U./ml. in myocardial infarction but reaches peaks as high as those of SGO-T and SLDH in active liver disease (frequently over 1,000 U./ml.).

RESULTS

Table I illustrates the results of the SGO-T, SLDH, and SGP-T determinations in the 20 cases studied.

Whereas there is variation in the times at which the blood samples were drawn in the preoperative and the three postoperative periods, the selected periods of sampling should provide maximum opportunity for discovering abnormally elevated levels of serum enzymes in characteristic curve patterns.

The operative procedures have been divided into three groups: Group A—laparotomies (Cases 1 through 13); Group B—other major surgical procedures, not laparotomies (Cases 14 through 17); and Group C—minor surgical procedures (Cases 18 through 21). In only 3 cases were certain of the serum enzyme levels repeatedly abnormal. In Case 13 hepatic disease seemed an obvious preoperative complication; both SGO-T and SGP-T were elevated in the early specimens and returned to normal with drainage of the biliary tract. In Case 14 myocardial infarction ensued early in the postoperative course and a characteristic curve developed for all three enzymes. A secondary late rise of SLDH may have been the result of pulmonary embolism. In Case 17, a pneumonectomy, the SGO-T was moderately elevated on three postoperative days, not exhibiting the descending line of a curve. SLDH was low and SGP-T was normal.

One additional case, an hemorrhoidectomy, exhibited elevated SLDH, but not elevated SGO-T or SGP-T, on the second and third postoperative days.

TABLE I. EFFECT OF SURGICAL PROCEDURES ON SERUM ENZYME ACTIVITIES

CASE	OPERATION	ANESTHETIC		SGO-T	SLDH	SGP-T	ADDITIONAL DATA
A. Surgical Procedures Requiring Laparotomy							
1. M.H. F 45 yr. (MZH #112879)	Hysterectomy. Appendectomy	N_2O; Na Pentothal 2 hr. duration	*Preop. Postop. 1 2 3	11 — 23 20	136 — 101 132	34 — 16 11	Preop. BSP-0, Hb 12.4 Gm. %
2. A.S. F 68 yr. (MZH #112723)	Colostomy for carcinoma sign. with hepatic metastases	N_2O; Na Pentothal 2 hr.-10 min.	Preop. Postop. 1 2 3	30 20 23 14	92 111 — 230	13 12 — 9	Preop. Hb 8.2 Gm. % 1,500 ml. blood transfusion Postop. Hb 11.7 Gm. % Temp. 40° F. 2nd postop. day BSP-3%
3. L.H. M 50 yr. (MZH #113353)	Bilateral lumbar ganglionic sympathectomy for occlusive arteriosclerosis of legs	N_2O; Na Pentothal 2 hr.-30 min.	Preop. Postop. 1 2 3	20 17 20 8	182 175 189 135	28 18 21 12	BSP-5%
4. L.L. F 49 yr. (MZH #113600)	Abdominal resection of rectosigmoid for carcinoma	N_2O; Na Pentothal 3 hr.	Preop. Postop. 1 2 3	4 14 6 14	120 129 170 122	2 10 6 12	Preop. Hb 12 Gm. %
5. H.M. F 55 yr. (MZH #113396)	Cholecystectomy for cholelithiasis	N_2O; Na Pentothal 1 hr.-20 min.	Preop. Postop. 1 2 3	8 — 14 17	179 — 163 152	23 — 16 21	Preop. Hb 14 Gm. %
6. F.W. M 74 yr. (MZH #114114)	Gastrectomy for carcinoma. Repair of hiatal hernia	N_2O; Na Pentothal 3 hr.-15 min.	Preop. Postop. 1 2 3	8 31 38 31	74 130 108 166	8 19 17 15	Preop. Hb 10.6 Gm. % 1,500 ml. blood transfusion Postop. Hb 15 Gm. %
7. S.B. F 60 yr. (MZH #114044)	Abdominal perineal resection for carcinoma of rectum	N_2O; Na Pentothal 3 hr.	Preop. Postop. 1 2 3	16 20 28 14	228 112 118 170	13 14 17 7	Preop. Hb 13.5 Gm. % Myocardial infarction 1yr. prior, with no sequelae Mild diabetes

8. A.Z. F 76 yr. (MZH #125367)	Cholecystectomy for cholelithiasis	N_2O; Na Pentothal; Anectine 1 hr.-10 min.	Preop. Postop. 1 2 3	11 11 — —	136 130 — —	— — — —	Preop. Hb 12 Gm. %
9. B.C. F 7 yr. (MZH #125218)	Cholecystectomy for cholelithiasis. Ventral hernia repaired	N_2O; Na Pentothal; Anectine 2 hr.-25 min.	Preop. Postop. 1 2 3	14 26 20 20	110 146 172 237	— — — —	Preop. Hb 14 Gm. %
10. N.K. F 50 yr. (MZH #125863)	Hysterectomy for fibromyomata	N_2O; Na Pentothal 2 hr.-50 min.	Preop. Postop. 1 2 3	8 27 16 8	74 172 176 120	— — — —	Preop. Hb 11.7 Gm. % 1,000 ml. blood transfusion Postop. Hb 14.6 Gm. %
11. A.L. F 67 yr. (MZH #126389)	Cholecystectomy for cholelithiasis. Repair of cholecysto-duodenal fistula	N_2O; Demerol; curare 3 hr.-30 min.	Preop. Postop. 1 2 3	0 11 14 27	160 — 220 150	— — — —	Preop. Hb 14.5 Gm. %
12. A.L. M 33 yr. (MZH #126949)	Appendectomy for recurrent appendicitis	N_2O; Demerol; curare 1 hr.-15 min.	Preop. Postop. 1 2 3	0 2 0 11	145 107 103 170	— — — —	Preop. Hb 13 Gm. %
13. L.V. F 70 yr. (MZH #114183)	Sigmoidectomy. Cholecystojejunostomy for biliary obstruction from carcinoma of sigmoid and pancreas	N_2O; Na Pentothal 2 hr.-50 min.	Preop. Postop. 1 2 3	144 100 23 —	129 168 110 —	171 150 15 —	Preop. Hb 12.5 Gm. %

B. Major Surgical Procedures—Not Laparotomy

14. H.W. M 51 yr. (MZH #105028)	Repair of strangulated inguinal hernia with appendectomy	N_2O; procaine 1 hr.-50 min.	Preop. Postop. 6° 15° 31° 3-d 4-d 7-d	— 55 90 74 85 68 42	— 182 324 239 241 268 240	— 41 28 32 18 32 29	Preop. Hb 15.2 Gm. % Rh. Mitral insufficiency, Hypertension Shock 1st postop. day and Norep. I-V 24° ECG: Anterolateral myocardial infarction Pul. infarct 2nd postop. day Died 31st postop. day

TABLE I.—Cont'd

CASE	OPERATION	ANESTHETIC		SGO-T	SLDH	SGP-T	ADDITIONAL DATA
15. C.S. M 70 yr. (MZH #125889)	Suprapubic prostatectomy for benign prostatic hypertrophy	Spinal Pontocaine 1 hr.-20 min.	Preop. Postop. 1 2	27 — 27	— — —	— — —	
16. S.C. M 50 yr. (MZH #127837)	Thoracotomy for excision of chondroma of lung	N_2O; Na Pentothal; Anectine 2 hr.-15 min.	Preop. Postop. 1 2 3	14 32 27 32	69 108 120 107	— — — —	Preop. Hb 13.2 Gm. %
17. A.B. M 37 yr. (MZH #13000)	Thoracotomy for pneumonectomy for bronchiectasis	Na Pentothal; Anectine 5 hr. N_2O; curare	Preop. Postop. 1 2 3	— 64 64 78	— 79 75 93	— 26 34 20	Preop. Hb 14.2 Gm. % 2,500 ml. blood transfusion Postop. Hb 11.4 Gm. %
		C. Lesser Surgical Procedures					
18. D.B. F 44 yr. (MZH #113491)	Hemorrhoidectomy for extensive hemorrhoids	Procaine saddle block 45 min.	Preop. Postop. 1 2 3	6 8 6 27	114 148 282 429	12 9 9 14	Preop. Hb 13.6 Gm. % BSP-11% Liver slightly enlarged
19. B.F. F 77 yr. (MZH #114016)	Uterine curettage for endometritis	N_2O; Na Pentothal 1 hr.-5 min.	Preop. Postop. 1 2 3	11 14 14 12	120 192 152 107	14 7 19 8	Preop. Hb 14 Gm. % BSP-2%
20. O.D. F 49 yr. (MZH #114019)	Dental extraction; alveolectomy	N_2O 1 hr.	Preop. Postop. 1 2 3	6 14 11 —	187 118 125 —	8 13 5 —	Preop. Hb 10.9 Gm. % BSP-0
21. F.A. F 34 yr. (MZH #114272)	Bilateral ligation and stripping varicose veins of legs	N_2O; Demerol; curare 3 hr.-10 min.	Preop. Postop. 1 2 3	1 11 2 8	— — — —	— — — —	Preop. Hb 11.7 Gm. %

*Preop.—Blood drawn within 3 days before operation.
Postop. 1—Blood drawn between 6 and 20 hours after surgery.
2—Blood drawn between 24 and 48 hours after surgery.
3—Blood drawn between 48 and 72 hours after surgery.

Although the abnormal BSP test indicated that prior liver disease was probably present in this patient, the normal SGO-T and SGP-T suggested that venous thrombosis and escape of blood into connective tissue accounted for the rise in SLDH during the postoperative period.

Case 6 exhibited a single borderline abnormal SGO-T level of 38 U./ml., which level has been observed infrequently in normal individuals. Although falling within normal ranges of serum activity for the three enzymes, Cases 1 and 7 presented timed curves for SGO-T, and Case 10 for SGO-T and SLDH. A descending curve in normal ranges of SGO-T and SGP-T was observed in Case 3. Ascending curves within normal ranges were obtained in Cases 6, 9, 13, 18, and 21. In 2 of these cases, Cases 18 and 21, venous thrombosis was probably implicated. These minor serum enzyme changes may have been caused by the several surgical procedures.

It is of interest, although no explanation can be offered, that whereas the lowest normal levels of SGO-T are generally given as 5 U./ml., in Case 21 levels of 1 and 2 U./ml. were found, and in Cases 11 and 12 no SGO-T activity could be determined in certain specimens. SLDH was found at unusually low levels, below 100 U./ml., in Cases 2, 6, 10, 16, and 17. In these 5 cases the hemoglobin was below 12 Gm. per cent, and the elevations following transfusion were paralleled by increases of SLDH to normal levels.

Apparent correlation of anemia with low SLDH activity occurred in 4 cases and has been observed personally in 2 other patients with melena. Anemia with normal SLDH was observed in Case 20, and low SLDH without anemia was noted in Case 16, indicating that this association is not uniform.

DISCUSSION

Skeletal muscle was transected and to some degree ligated in all 17 operative procedures in Groups A and B of Table I. As has been reported by other observers,[14-16] moderate trauma and necrosis of muscle does not cause significant elevation of SGO-T, SLDH, or SGP-T, nor did it occur as a result of these surgical procedures. One patient, Case 17, exhibited an elevation of SGO-T to 64, 64, and 78 units on the first, second, and third postoperative days after a left pneumonectomy. This pattern did not follow the curve of rapid rise and fall of SGO-T that is characteristic of myocardial infarction. SLDH was low, 79, 75, and 93 units, as found in other anemic patients, and SGP-T was normal throughout. In all three groups of Table I various other tissues were damaged. The type of operative procedure did not seem to modify the serum enzyme responses, except for one pneumonectomy. The limited types of anesthetic agents employed, namely nitrous oxide, Anectine, Sodium Pentothal, and procaine locally or in "spinal" or saddle block anesthesia, did not apparently influence the serum enzyme levels by acute hepatic injury or damage to other tissues. The duration of anesthesia was not correlated with alteration of these serum enzyme activities.

Quiescent chronic hepatic disease generally does not cause elevation of SGO-T, SLDH, or SGP-T.[21,22] This is confirmed by the normal enzyme activity in Case 3 with 5 per cent retention of BSP in one hour, and of normal SGO-T

3—Blood drawn between 48 and 72 hours after surgery.

and SGP-T in Case 18. The latter case exhibited a single borderline high SLDH, but this rise probably cannot be attributed to active hepatic disease since SGO-T and SGP-T are, generally, equally sensitive indices of hepatocellular damage.

CONCLUSIONS

1. In 18 of 21 miscellaneous surgical procedures, 17 major operations with skeletal muscle incision and dissection, and 4 lesser surgical operations, no significant postoperative elevation of the serum enzymes SGO-T, SLDH, and SGP-T occurred. One patient exhibited a moderate elevation of SGO-T but not of SLDH or SGP-T after a left pneumonectomy. The SGO-T timed curve did not resemble that of myocardial infarction. One patient with initial hepatic damage exhibited high SGO-T and SGP-T levels, and one case was complicated by a fatal myocardial infarction. The latter patient exhibited curves of elevated SGO-T and SLDH, with slight rises of SGP-T, characteristic of that lesion.

2. Surgical procedures, as illustrated by this limited series, will not cause sufficient elevations of SGO-T and SLDH to mask the characteristic curve exhibited by a major myocardial infarction which is complicating the operative or postoperative course of a patient.

3. There were certain fluctuations in the degree of activity of these enzymes within the present standards of normal and certain instances of minimal abnormal levels, which possibly have a significant, but currently unknown, relationship to the surgical procedures. Anemia has some correlation with low SGO-T and SLDH activities.

We are indebted to Dr. J. Abouav, Dr. A. L. Brown, Dr. M. M. Culiner, and Dr. L. D. Rosenman for observation of the surgical cases, and to Dr. A. E. Lewis, Mr. E. D. Hill, and Mr. R. N. Mann for performance of the serum enzyme determinations.

REFERENCES

1. LaDue, J. S., Wroblewski, F., and Karmen, A.: Science **120**:497, 1954.
2. Wroblewski, F., and LaDue, J. S.: Proc. Soc. Exper. Biol. & Med. **90**:210, 1955.
3. Wroblewski, F., and LaDue, J. S.: Proc. Soc. Exper. Biol. & Med. **91**:569, 1956.
4. Sampson, J. J.: Progress in Cardiovas. Dis. **1**: No. 2. (In press)
5. White, L. P.: New England J. Med. **255**:984, 1956.
6. Wroblewski, F., and LaDue, J. S.: J.A.M.A. **150**:1212, 1952.
7. Siegel, A., and Bing, R. J.: Proc. Soc. Exper. Biol. & Med. **91**:604, 1956.
8. Nydick, I., Wroblewski, F., and LaDue, J. S.: Circulation **12**:161, 1955.
9. Agress, C. M., Glassner, H. F., and Binder, M. J.: Proc. Soc. Exper. Biol. & Med. **92**:826, 1956.
10. Lemley-Stone, J., Merrill, J. M., Grance, J. T., and Maneely, G. R.: Am. J. Physiol. **183**:555, 1955.
11. LaDue, J. S.: J.A.M.A. **165**:1776, 1957.
12. Ostrow, B. H., Steinberg, D., Ticktin, H. E., Polis, G. N., and Evans, J. M.: Circulation **14**:790, 1956.
13. Lawrence, S. H., and Schulkins, T.: Anesthesiology **17**:531, 1956.
14. Merrill, J. M., Lemley-Stone, J., Grace, J. T., Jr., and Maneely, G. R.: J.A.M.A. **160**:1454-1456, 1956.
15. MacDonald, R. P., Simpson, J. R., and Nossal, E.: J.A.M.A. **165**:35, 1957.
16. Lieberman, J., Lasky, I. I., Dulkin, S. I., and Lobstein, O. E.: Ann. Int. Med. **46**:485, 1957.
17. Ticktin, H. E., Ostrow, B. H., and Evans, J. M.: Clin. Res. Proc. **4**:102, 1956.
18. Karmen, A.: J. Clin. Invest. **34**:131, 1955.
19. Wroblewski, F., and Cabaud, P.: Am. J. Clin. Path. **27**:235, 1957.
20. Cabaud, P., Leeper, R., and Wroblewski, F.: Quoted by Wroblewski and Cabaud.[19]
21. Wroblewski, F., and LaDue, J. S.: Ann. Int. Med. **45**:801, 1956.
22. Horn, H. D., and Amelung, D.: German Medical Monthly **3**:46, 1958.

A Study of the Influence of Tropical Weather on Output of Volume, Work, and Power by the Right and Left Ventricles of Man at Rest in Bed

George Burch, M.D., and Albert Hyman, M.D., New Orleans, La.

It has been shown previously[1] that a hot and humid climate will increase greatly the output of volume, work, and power of the right and left ventricles of normal man at rest, and only slightly increase that of patients with chronic congestive heart failure. The levels of heat and humidity employed in those studies were high in order to produce definite contrast.[1] The elimination of excess body heat increases the work of the heart, especially in a hot and humid environment in which elimination of heat is difficult. Because of the marked increase in work by the heart produced by the *hot* and humid environment, it was considered important to know whether or not *warm* and humid tropical weather also would increase the work of the heart of patients at rest in bed. In order to answer this problem, and because of its importance in the treatment of patients with heart disease, it was decided to study the work of the heart of patients at rest in bed in the wards at the Charity Hospital in New Orleans, during the tropical climate of mid-summer (August, 1957). For contrast, the same patients were also studied in a cool and comfortable air-conditioned ward or neutral environment. This report describes briefly the results of these investigations.

TABLE I. SUMMARY OF CLINICAL DATA ON 5 HOSPITALIZED NEGRO PATIENTS WITHOUT HEART DISEASE WHO WERE STUDIED IN ORDER TO LEARN THE INFLUENCE OF TROPICAL WEATHER ON CARDIAC OUTPUT

SUBJECT NUMBER	AGE	SEX	DIAGNOSIS	TREATMENT	TEMPERATURE			RELATIVE HUMIDITY*	
					MAX. (°F.)	MIN. (°F.)	MEAN (°F.)	MAX. (%)	MIN. (%)
1.	41	M	Lesion, right middle lobe, etiology undetermined	Streptomycin, penicillin	88	77	83	87	47
2.	63	F	Diabetes mellitus	Orinase	91	74	83	96	63
3.	42	F	Diffuse colloid nontoxic goiter	Lugol's sol., thyroid	94	79	87	92	46
4.	48	M	Osteoarthritis, cervical spine	ASA	90	76	83	70	41
5.	54	F	Rheumatoid arthritis	Symptomatic	95	78	87	91	43
Mean	50				92	77	85	87	48

*New Orleans weather at Post Office Station, U.S. Weather Bureau.

From the Department of Medicine, Tulane University School of Medicine, and Charity Hospital of Louisiana, New Orleans, La.

Aided by grants from the Public Health Service (H-143), the Upjohn Company, Kalamazoo, Mich., and the Thibodeaux Research Foundation.

Received for publication Oct. 14, 1958.

METHODS AND MATERIALS

Five adult volunteer patients without cardiac disease were studied. Their pertinent clinical data are summarized in Table I. The studies were conducted from 12:30 to 2:30 P.M. All subjects had had breakfast prior to 8:00 A.M., and all remained at rest in bed from breakfast until the time of the study. They were placed on a roller for the studies in order to facilitate movement from one environment to the other. The cardiac output and right ventricular pressure curves were obtained by means of right heart catheterization without x-ray visualization but with pressure recording for guidance and placement of the catheter. Brachial arterial blood pressure was recorded directly by means of a transducer and pressure recorder. Respiratory rate and pulse

TABLE II. INFLUENCE OF TROPICAL WEATHER ON CARDIAC OUTPUT. SUMMARY OF DATA OBTAINED ON 5 HOSPITALIZED ADULT PATIENTS AT REST IN BED

SUBJECT*	ROOM TEMP. (°F.)	R.H. (%)	BLOOD PRESSURE		PULSE (PER MIN.)	RESP. (PER MIN.)	O_2 CONSUMPTION (C.C./MIN.)	A-V O_2 DIFFERENCE (C.C./100 C.C.)	C.O. (L./MIN.)	STROKE VOL. (C.C.)
			SYSTOLIC (MM. Hg)	DIASTOLIC (MM. Hg)						
			Comfortable Environment							
1.	74	47	135	85	58	—	179	3.8	4.7	80
2.	76	67	128	82	92	24	139	3.8	3.6	40
3.	72	49	165	100	106	17	259	4.0	6.4	56
4.	—	—	96	70	68	—	52	3.3	1.6	26
5.	72	60	135	75	88	24	151	2.3	6.5	73
Mean	74	56	132	82	82	22	156	3.4	4.6	55
			Warm and Humid Environment							
1.	92	76	135	80	60	13	365	5.7	6.4	103
2.	91	65	120	84	104	28	149	3.0	5.0	53
3.	91	58	125	77	101	17	250	3.2	7.8	65
4.	—	—	103	62	64	26	153	4.0	3.9	62
5.	99	70	126	74	88	20	222	2.6	8.6	97
Mean	93	67	123	75	83	21	228	3.7	6.3	76

*Subjects 1 and 2 were studied on the hot ward first and then moved to the cold ward. Subjects 3, 4, and 5 were studied on the cold ward first and then moved to the hot ward, although they were originally from hot wards.

TABLE III. INFLUENCE OF TROPICAL WEATHER ON CARDIAC OUTPUT IN 5 HOSPITALIZED ADULT PATIENTS AT REST IN BED

SUBJECT NUMBER	COOL WARD (L./MIN.)	WARM WARD (L./MIN.)	INCREASE (PER CENT)
1.	4.7	6.4	36
2.	3.6	5.0	39
3.	6.4	7.8	22
4.	1.6	3.9	144
5.	6.5	8.6	32
Mean	4.6	6.3	37

rate were measured simultaneously with the recording of pressure in the right ventricle. Two studies were conducted with the patients in the air-conditioned ward first, and then repeated with the subjects in the warm humid ward after they had rested at least an hour in the new environment. The remaining three studies were made with the subjects first in the warm and humid ward and then in the comfortably cool air-conditioned ward, where they remained for about one hour before the study was repeated.

Except for the pressure of the right ventricle, which was recorded directly, the time-course curves of pressure, volume, pressure-volume diagrams, accumulated work and power were calculated for the right and left ventricles as previously described.[2,3] The same assumptions were made here and, of course, were subject to the limitations indicated previously.[1,2]

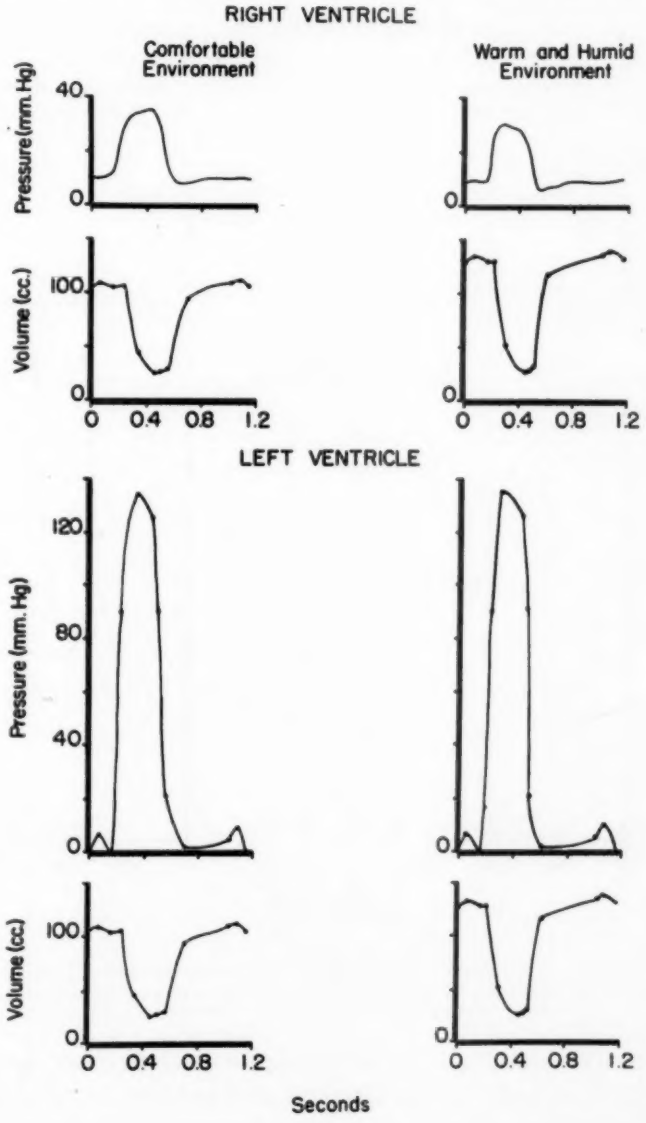


Fig. 1*A*.—Time-course curves of pressure and volume for Subject No. 1 resting in a comfortably cool air-conditioned ward and in a warm and humid open ward during the tropical weather of New Orleans, summer, August, 1957. These environmental conditions are referred to in all illustrations to follow.

RESULTS

The results are summarized in Tables II and III and Figs. 1, 2, and 3.

The average cardiac output was 37 per cent greater in the warm and humid atmosphere or tropical weather than in the comfortably cool air-conditioned atmosphere (Tables II and III). The individual variations were fairly large, but output was consistently greater in all 5 subjects studied (Tables II, III). The increase in output was obtained mainly by a greater stroke volume, but in part by an increase in cardiac rate.

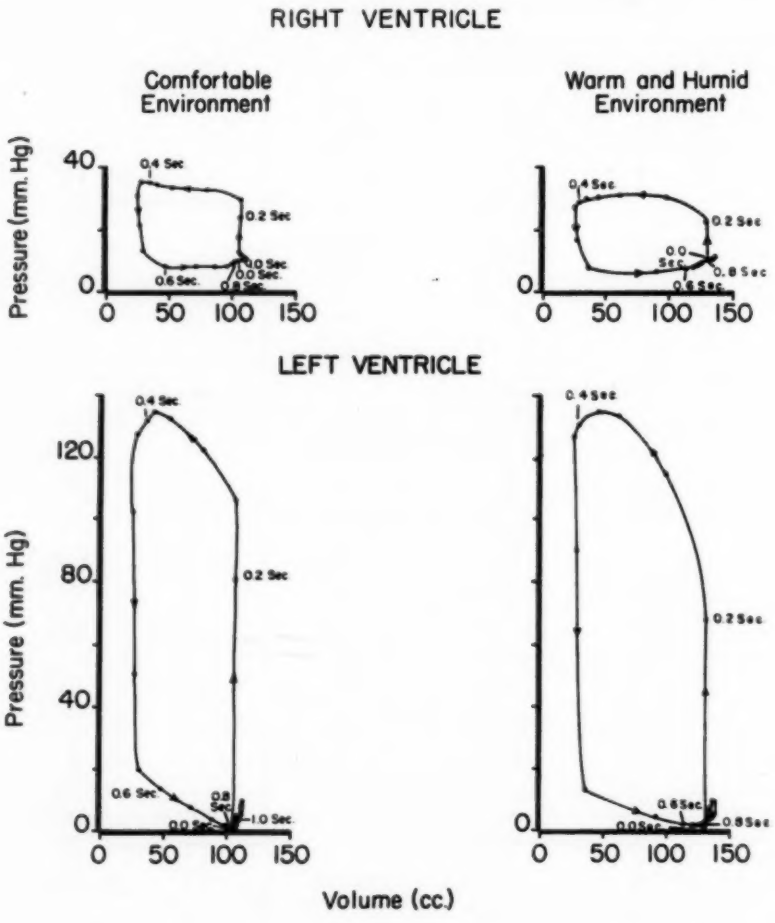


Fig. 1*B*.—Pressure-volume-time diagram calculated for the curves shown in Fig. 1*A*. The increase in work of the two ventricles produced by the tropical weather is evident.

The calculated pressure-volume diagrams, work and power curves showed the *left ventricle* to do more work in the tropical atmosphere in every instance except for Subject No. 3. In this subject, even though cardiac output and stroke volume were greater in the warm and humid atmosphere, systemic arterial blood pressure was lower, resulting in slightly less work and power output of the left ventricle (Fig. 2).

The calculated pressure-volume diagram, work and power curves (Figs. 1*A*, 1*B*, and 1*C*) showed the *right ventricle* to perform greater work in the warm and humid environment in three subjects, less work in one subject (Subject No. 3) (Fig. 2), and no difference in work in the other subject (Fig. 3). Since all subjects had a greater stroke volume and cardiac output in the warm and humid atmosphere, it was the associated decline in pulmonary arterial blood pressure that resulted in less work being performed by the right ventricle of Subject No. 3, and no change in work in Subject No. 2. The latter subject had a disproportionately lesser decline in systemic arterial blood pressure as compared to pulmonary

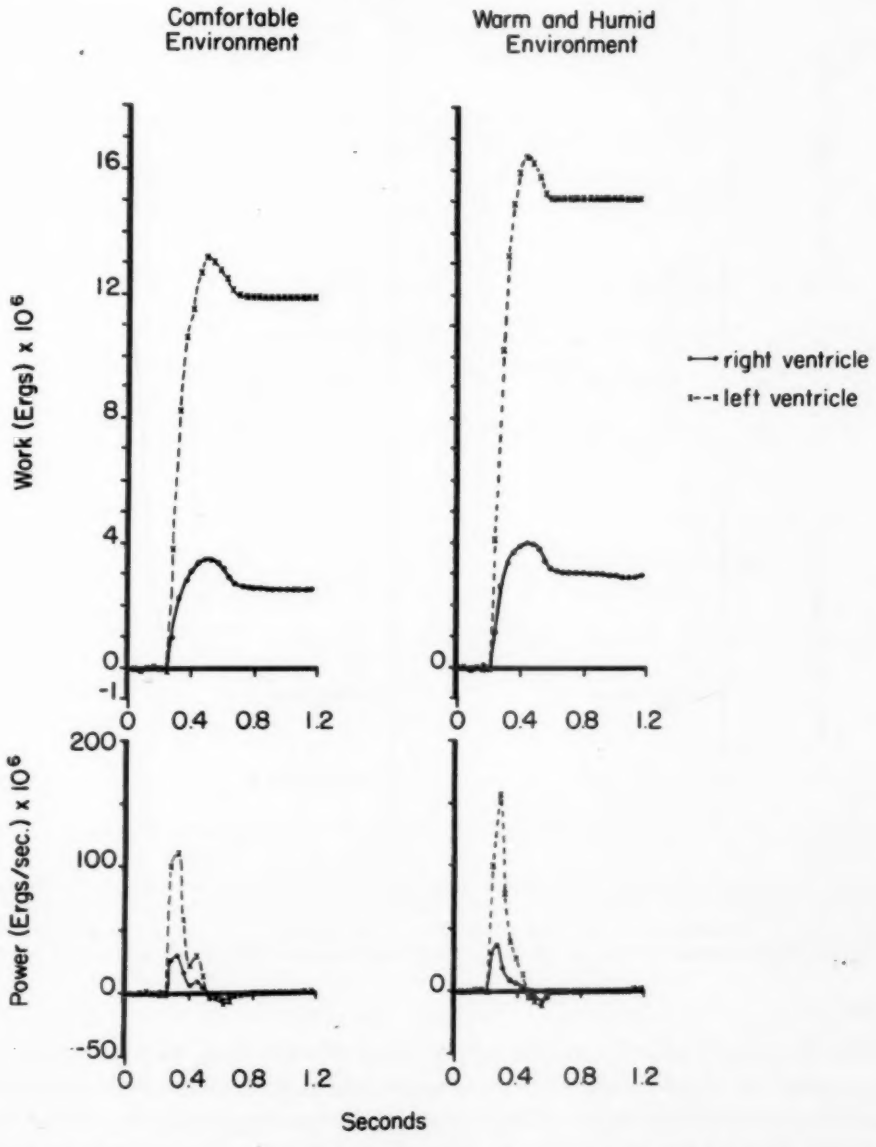


Fig. 1*C*.—Time-course curves of accumulated work and power calculated from the pressure-volume diagrams shown in Fig. 1*B*. The tropical weather produced an increase in work and power output of both ventricles.

arterial blood pressure, so that even though both ventricles were ejecting the same volume of blood, the left ventricle was performing more work in the warm and humid environment than in the cool environment, whereas the right ventricle performed the same amount of work in both the warm and humid and the cool environments (Fig. 3).

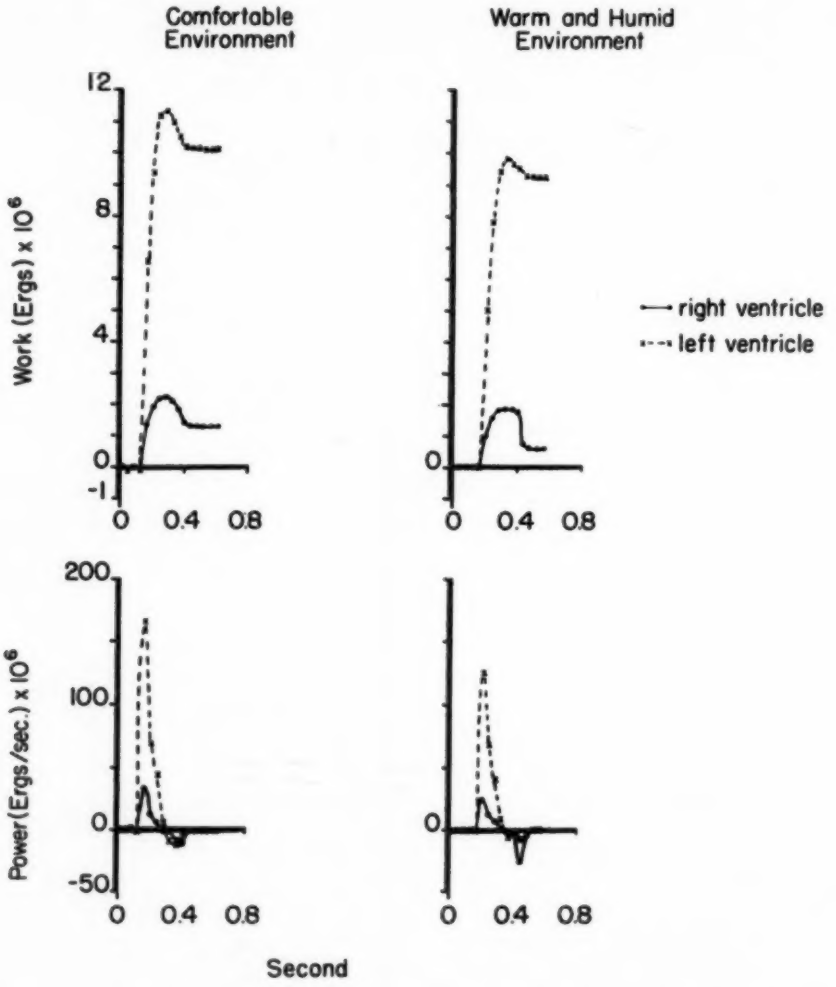


Fig. 2.—Calculated time-course curves of accumulated work and power output of the right and left ventricles of Subject No. 3 resting in a comfortably cool air-conditioned ward and in a ward open to tropical weather. Although stroke volume was greater for the tropical weather, systemic and pulmonary arterial pressures were less, so that the work output of the two ventricles was even less.

DISCUSSION

The illustrations indicate the importance of recording the pressure-volume diagram and the time-course curves of work and power for a single cardiac cycle for each chamber of the heart. Cardiac output alone does not indicate the work of the heart. Except for the pressure curve of the right ventricle, it was necessary to make gross assumptions to obtain these various time-course curves. Until the volume- and pressure-time-course curves can be obtained directly and ac-

curately, *calculated* curves, as shown, must be considered cautiously. They show roughly, but satisfactorily, the nature of the problems involved in measuring the output of work and power of the chambers of the heart. It is obvious that satisfactory, direct, continuous recording of pressure and of volume during each pulse cycle of the cardiac chambers under study must provide accurate temporal relationships for these two parameters. This is necessary for satisfactory evaluation of the time course of work and power output of the chambers. The curves described lack accurate temporal relationships because of the nature of the assumption and calculations.

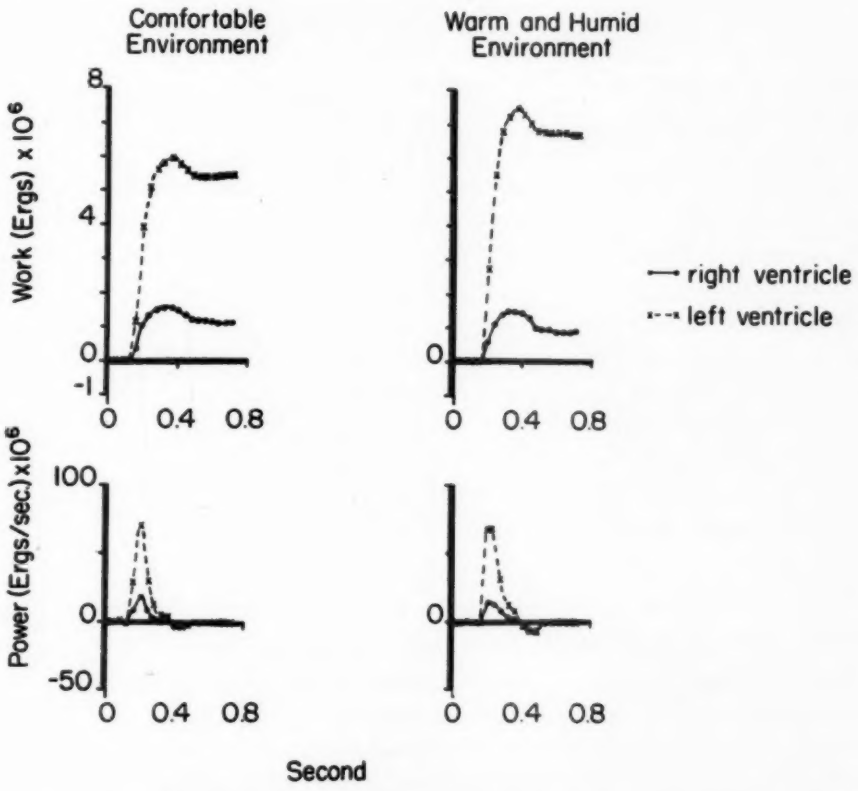


Fig. 3.—Calculated time-course curves of accumulated work of the left and right ventricles of Subject No. 2 resting in a comfortably cool air-conditioned ward and in a ward open to tropical weather. Although the work output of the left ventricle increased in the warm and humid environment, that of the right ventricle did not, in spite of an increase in stroke volume, because of a decline in pulmonary arterial pressure without an associated decline in systemic arterial blood pressure. Thus, both ventricles can increase in stroke volume output without there being an equal, if any, increase in output of work.

Obviously, mean values for stroke volume or cardiac output are not sufficient. These studies show how a ventricle may increase its stroke volume without increasing its work when there is an associated decline in pressure. It was properly assumed that both ventricles eject equal volumes of blood if the circulation is normal and stable. However, Fig. 3 shows a subject in whom the left ventricle performed more work in the warm and humid atmosphere than in the cool one, while at the same time the right ventricle performed the same amount of work

in both environments even though the Fick measurements of cardiac output showed a greater output for both ventricles in the warm and humid atmosphere. Thus, a greater cardiac output does not necessarily indicate a greater output of work and of power for both or either of the ventricles. These important problems as well as other obvious ones cannot be answered satisfactorily until a reliable method is developed to measure continuously the time course of volume change of chambers of the heart under study.

Again, even with the limitations in accuracy and the relative crudeness of the Fick method of right heart catheterization for measurement of cardiac output, all subjects had a greater cardiac output in the warm and humid environment than in the comfortably cool one. These findings indicate again[1-3] the increase in cardiac output and the increase in work usually produced by a warm and humid environment, and also show the benefits of air-conditioning upon the heart, favoring rest of the heart. The subjects studied were "acclimated," having lived in New Orleans throughout the spring and summer. Surely, with proper acclimatization people can adjust considerably to a warm and humid environment. Obviously, these subjects, although acclimatized, had not adjusted fully to the summer weather. These studies indicate further that the condition of the atmosphere in which a patient lives must be given proper consideration in therapy.

Although the influence of physical work performed by the skeletal muscles was not investigated in these experiments, other studies and experiences in the comfortably cool and hot and humid atmospheric conditions indicate that there is even greater stress upon the cardiovascular system in the warm and humid environment when the subject exerts himself than when he is at rest. Although the studies were conducted on chronically ill patients, the trends in the findings most probably apply to normal people as well.

SUMMARY

Studies of 5 volunteer patients without congestive heart failure at rest in bed in the hospital showed a 37 per cent increase in the mean cardiac output in the tropical weather during mid-summer in New Orleans (August, 1957) over that in a comfortably cool air-conditioned atmosphere. The calculated time-course curves of the pressure-volume diagram, work, and power revealed the superiority of such recordings over the conventionally obtained mean volumes of cardiac output as indices of cardiac work. These curves indicate the need of a reliable method for recording the time course of volume change of each chamber of the heart during a single cardiac cycle.

If it is desirable to maintain the heart at rest in the treatment of patients with heart disease, the atmosphere of the patient's sickroom should be cool and comfortable.

REFERENCES

1. Burch, G. E., and Hyman, A.: Am. Heart J. 53:665, 1957.
2. Burch, G. E., Ray, C. T., and Cronvich, J. A.: Circulation 5:504, 1952.
3. Burch, G. E.: J. Chron. Dis. 4:350, 1956.

An Abnormal Electrocardiographic Pattern and Its Relation to Ventricular Fibrillation (Observations During Clinical and Experimental Hypothermia)

Antonio Boba, M.D., Albany, N.Y.

Sixty hypothermic patients have been observed at the Albany Hospital during the last 2 years. Continuous electrocardiographic monitoring, by means of an oscilloscope coupled to a direct writer, has been a part of the routine management in all cases. Our attention was attracted by a peculiar wave which seemed to appear at rather low temperatures and persist until the body temperature returned to a more comfortable level of hypothermia (Table I). Once the body temperature had returned to normal, this wave was not seen again, and the follow-up failed to demonstrate its reappearance.

This wave is of low voltage, of a duration equal to or greater than the QRS complex, and it appears immediately after the ventricular complex, frequently impinging upon it (Fig. 1). This accident was observed in 9 of the 60 patients, and in each instance it discouraged further cooling for fear of the predisposing effects of deeper hypothermia to ventricular fibrillation.

TABLE I. CLINICAL OBSERVATIONS

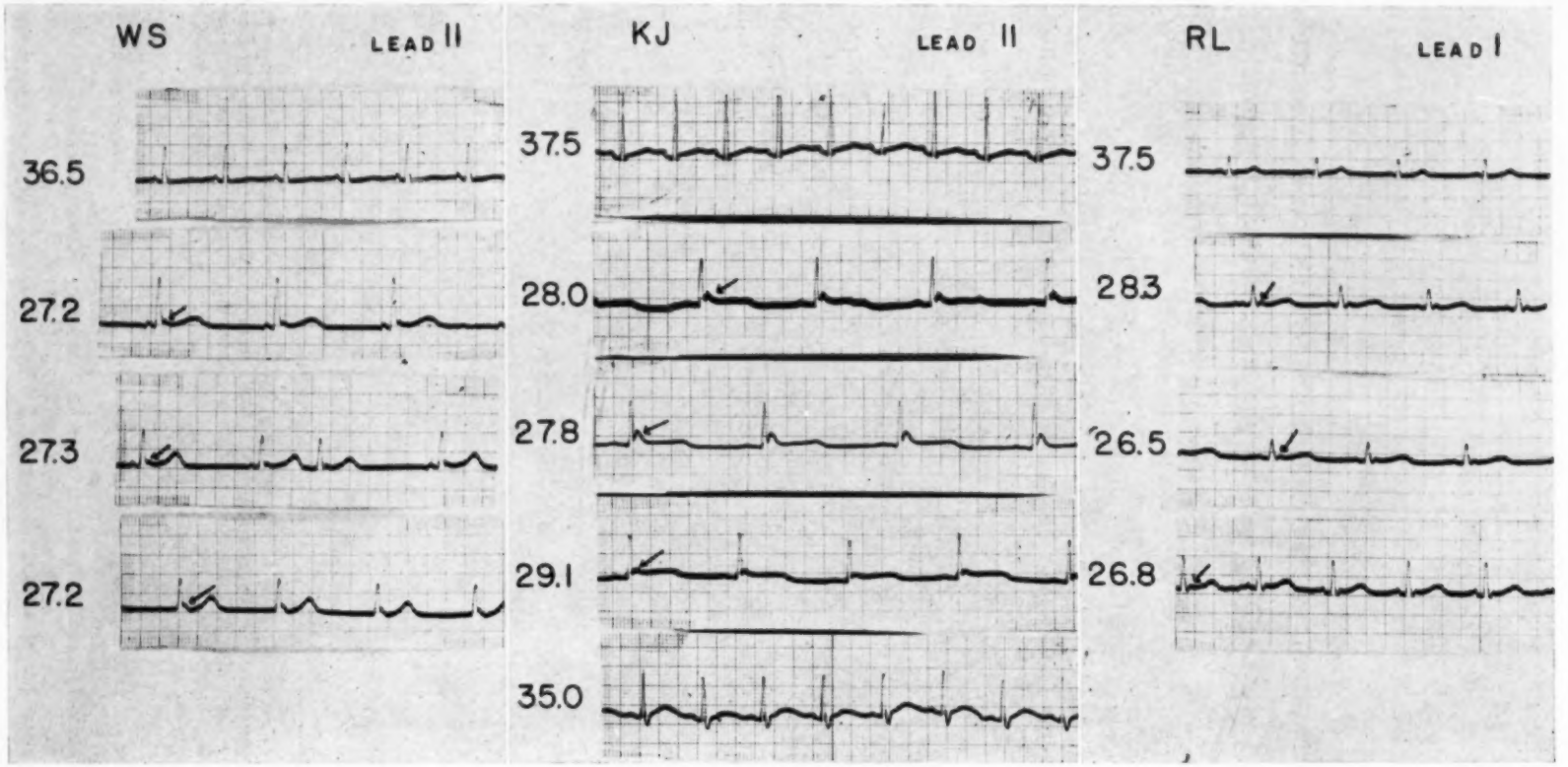
NUMBER	PATIENT	APPEARANCE*	MINIMUM*	DISAPPEARANCE*
1.	A.R.	27.0	25.0	29.0
2.	K.J.	28.8	27.8	30.9
3.	J.J.	28.5	27.0	29.5
4.	L.B.	29.0	27.0	31.0
5.	C.D.	29.3	24.5	27.2
6.	C.C.	28.6	28.5	29.8
7.	E.D.	29.8	26.8	31.6
8.	R.L.	28.3	25.8	Not recorded
9.	A.P.	31.0	29.2	Not recorded

*Rectal temperatures, in centigrades, at which the abnormal electrocardiographic wave is first seen, lowest temperatures achieved, and temperature at which the wave disappears. With one exception only, the temperature at which the abnormal pattern was first observed was below 30.0°C. As a general rule the abnormal pattern persisted until the temperature had come back to slightly above the temperature at the time of its appearance.

From the Department of Anesthesiology, the Albany Medical College of Union University, and the Albany Hospital, Albany, N.Y.

This work was supported entirely by Grant 243 from the Committee on Research of the American Medical Association.

Received for publication Oct. 17, 1958.



A. *B.* *C.*

Fig. 1.—*A*, W. S., a patient undergoing hypothermia for removal of a large intracranial vascular tumor. The abnormal wave was detected first at a body temperature of 27.5°C., but it became quite clear at a body temperature of 27.2°C. (second strip from top). It remained unchanged as long as the temperature remained low (third and fourth strips), and it disappeared completely upon rewarming. *B*, K. J., a patient undergoing hypothermia as part of the management of brain-stem injury after a car accident. Notice how the wave becomes more prominent as the body temperature falls, and fades out as the temperature returns toward normal. This patient lived 24 hours after return of body temperature to normal, and repeated electrocardiograms showed regular sinus rhythm. *C*, R. L., a patient undergoing hypothermia for intracranial aneurysm. Notice appearance of the wave at a body temperature of 28.3°C. In this case the body temperature was allowed to fall to 26.5°C. without any obvious changes in the appearance of the electrocardiogram. Upon rewarming, the abnormal wave disappeared completely.

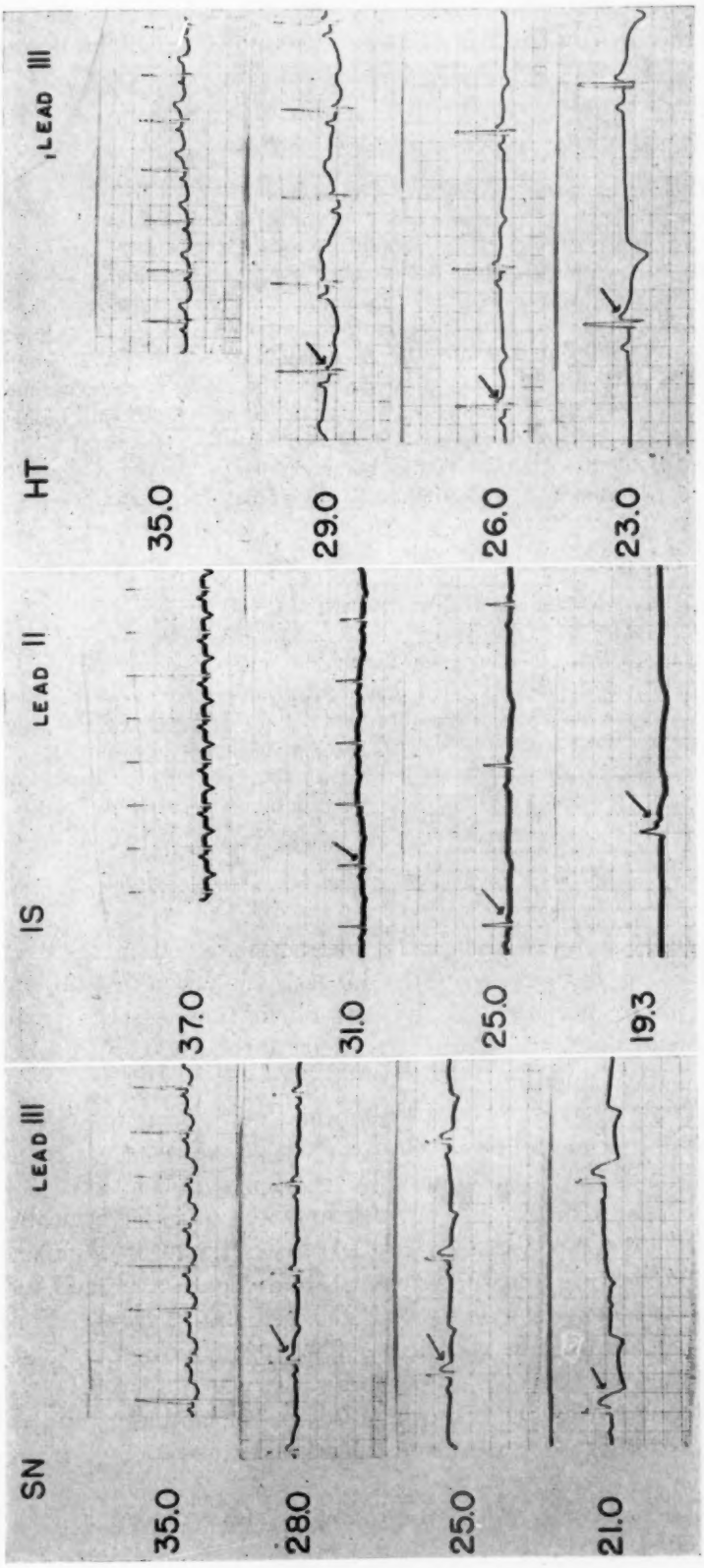


Fig. 2.—Electrocardiographic tracings from experimental animals. In these cases immersion was continued until death. Notice how the wave becomes more and more pronounced as the temperature falls. All of these animals died in ventricular fibrillation.

The possibility that this particular pattern was a constant and reliable premonitory sign of ventricular fibrillation has stimulated the following laboratory investigation.

MATERIAL AND METHODS

Seventeen adult, splenectomized, mongrel dogs weighing from 8 to 16 kilograms were employed for this study. They were anesthetized with intravenous Nembutal, 60 mg./Kg., and endotracheal intubation was carried out with a cuffed No. 10 Portex tube. The femoral vein and artery of one side were cannulated, electrode plates for electrocardiographic recording were secured to the four extremities, and a rectal thermometer was inserted deeply and secured to the tail with a No. 3 braided silk stitch. (The gas expansion thermometer* was used throughout.) The venous cut-down was used for the administration of additional Nembutal as required to control shivering, and no other drug was used at any time in the course of the experiment. The arterial cut-down was connected, via a three-way stopcock, to a conventional U-shaped mercury manometer, and the side arm of the stopcock was used for the withdrawal of blood samples. After not less than 20 minutes from the time of induction of the anesthesia, base-line recordings were taken and hypothermia induced by immersion in a small tub containing ice water. The temperature of the water was checked at frequent intervals, and it never exceeded 3°C. Immersion in ice water was continued until the animal died.

The rectal temperature, the blood pressure, the arterial pH, the respiratory rate, and the electrocardiographic pattern were recorded at frequent intervals. With reference to the electrocardiographic pattern under investigation the body temperature at the time of its appearance and the body temperature at which ventricular fibrillation supervened were recorded separately.

Three groups of dogs were studied. The first group (7 animals) was allowed to breathe room air spontaneously, and no respiratory assistance was given at any time. The second group (5 animals) was hyperventilated with 100 per cent oxygen by means of an automatic ventilator.[1] The third group (5 animals) was hyperventilated with the same device, using a mixture of 10 per cent oxygen and 90 per cent nitrogen. Hyperventilation was carried out in the two groups up to the time of death.

RESULTS

Four of the 17 animals that were investigated died in cardiac standstill. The electrocardiographic pattern under investigation was not observed at any time in any of these animals. Ventricular fibrillation was the terminal event in the remaining 13 dogs, and it was preceded by the appearance of the electrocardiographic pattern under study in 12 cases.

The 12 animals which showed the abnormal wave prior to ventricular fibrillation were distributed as follows: *Group I (breathing room air spontaneously):* Four of the 7 animals in this group died in ventricular fibrillation. All 4 of them exhibited the electrocardiographic pattern under study. It was observed first at an average rectal temperature of 25°C. (range 21.5 to 29), and the gradient between this temperature and the temperature at death averaged 4.1°C. (range 2 to 7). *Group II (hyperventilated with 100 per cent oxygen):* Four of the 5 animals in this group died in ventricular fibrillation. All 4 of them exhibited the electrocardiographic pattern under study. It was observed first at an average rectal temperature of 28.5°C. (range 26 to 31), and the gradient between this temperature and the temperature at death averaged 10.8°C. (range 8 to 15)

*Cat. No. 57, manufactured by the J. P. Marsh Company, Skokie, Ill.

Group III (hyperventilated with 10 per cent oxygen and 90 per cent nitrogen): The 5 animals in this group died in ventricular fibrillation; however, the electrocardiographic pattern under study was observed in only 4 of them. In the 4 cases in which it was seen, it appeared first at an average rectal temperature of 28°C. (range 26 to 31), and the gradient between this temperature and the temperature at death averaged 12.3°C. (range 9.5 to 15.8).

TABLE II. EXPERIMENTAL OBSERVATIONS

	GROUP I (BREATHING ROOM AIR SPONTANEOUSLY)	GROUP II (HYPERVENTILATED WITH 100% OXYGEN)	GROUP III (HYPERVENTILATED WITH 10% OXYGEN AND 90% NITROGEN)
Appearance*	Average 25.0°C. Range 21.5–29	Average 28.5°C. Range 26–31	Average 28.0°C. Range 26–31
Gradient†	Average 4.1°C. Range 2–7	Average 10.8°C. Range 8–15	Average 12.3°C. Range 9.5–15.8

*"Appearance" signifies the rectal temperature at the time that the abnormal pattern was observed.
†"Gradient" signifies the difference in temperature between the time that the pattern was first observed and the time that ventricular fibrillation supervened.

TABLE III. ASSOCIATION OF THE ABNORMAL ELECTROCARDIOGRAPHIC PATTERN WITH VENTRICULAR FIBRILLATION

	FIBRILLATION		STANDSTILL		TOTAL
	WAVE	NO WAVE	WAVE	NO WAVE	
Group I (Breathing room air spontaneously)	4	—	—	3	7
Group II (Hyperventilated with 100% oxygen)	4	—	—	1	5
Group III (Hyperventilated with 10% oxygen and 90% nitrogen)	4	1	—	—	5
Total	12	1	—	4	17

This table shows the high degree to which the abnormal electrocardiographic pattern under study is associated with ventricular fibrillation.

These data are summarized in Tables II and III. The arterial blood pressure, the rectal temperature, and the pulse rate fell in a somewhat linear fashion throughout each experiment. The arterial pH varied widely, but at the time of death it was below 7.18 in all the animals that were breathing room air spontaneously, and above 7.30, and as high as 7.77, in the animals that were hyperventilated. These pH values were unrelated to the mode of death of the animals.

With the exception of some determinations of serum magnesium in 9 dogs, no other relevant observations were made and no other blood samples withdrawn.

DISCUSSION

The recent popularity of elective hypothermia during cardiovascular and neurosurgical procedures has resulted in the appearance of a voluminous literature on the subject of electrocardiographic changes at low body temperatures.[2-7] The appearance of an electrocardiographic disturbance similar to the one observed in our patients, even though previously reported,[8,9] has failed to attract attention. Furthermore, recent experimental work has shown that a low body temperature is not a necessary prerequisite for its appearance.[10] However, the fact that this wave was frequently observed at body temperatures which are within the fibrillatory range,[11] and the fact that at the present time there is no reliable premonitory sign of ventricular fibrillation,[12] have stimulated our interest in uncovering some correlation between its appearance and ventricular fibrillation under experimental conditions.

The results of our experimental work indicate a high degree of association between this wave and ventricular fibrillation; in fact, it was not seen at all in those animals which did not fibrillate, and it was observed in 12 of the 13 animals which did fibrillate (Table III).

The temperature at which it was first observed was fairly constant, independent of spontaneous breathing or hyperventilation with 100 per cent oxygen or a hypoxic mixture (Table II). Statistical comparison of the means fails to reveal significant differences between any of the three groups; $p > 0.01$ in all cases. The temperature gradients between the temperature at the time the abnormal wave is first seen and the body temperature at the time that ventricular fibrillation supervenes show some differences between the three groups (Table II). The gradient is smaller in the group breathing room air spontaneously and greater in the group being hyperventilated with an oxygen-poor mixture, while that of the group hyperventilated with 100 per cent oxygen lies somewhere in between. Statistical comparison of the means reveals $p < 0.01$ for the group breathing room air spontaneously and the group hyperventilated with 100 per cent oxygen. If the group hyperventilated with the oxygen-poor mixture is compared to the group breathing room air spontaneously, then $p < 0.001$. The arterial pH, the pulse rate, and the arterial blood pressure did not show any type of association with the wave under study.

Thus it would appear that hyperventilation increases the margin of temperature between the body temperature at which the abnormal wave is first observed and the temperature at which fibrillation supervenes. It would seem also that hyperventilation with an oxygen-poor mixture is better in this respect than hyperventilation with 100 per cent oxygen. This finding is rather startling, but it could be explained by the following argument. Mechanical hyperventilation, with the benefit of a nonrebreathing valve, will remove large amounts of

carbon dioxide from the blood, but it does not affect the rate at which carbon dioxide is unloaded by the cells into the blood stream. This rate is regulated by the pCO_2 gradient between the cells and the capillary blood and the availability of reduced hemoglobin. When a hypothermic subject is hyperventilated with 100 per cent oxygen, the amount of oxygen dissolved in the plasma increases considerably, while metabolic oxygen requirements decrease so that little if any of the hemoglobin is desaturated as it goes through the capillary bed. This is a situation similar to that seen when pure oxygen is breathed under high pressure. The use of an oxygen-poor mixture (in our experiment, 76 mm. Hg partial pressure in the inspired mixture), by allowing some of the hemoglobin to be desaturated at all times, could obviate this inconvenience.

Although none of the 9 patients (Table I) who exhibited the electrocardiographic pattern under consideration had progressed to ventricular fibrillation, and although our clinical experience with ventricular fibrillation has been limited to three instances, all occurring during circulatory arrest for correction of aortic stenosis, the result of these experiments has modified somewhat our conduct in the operating room. These modifications may now be summarized. The appearance of the wave under consideration in the electrocardiogram of a patient subjected to hypothermia is assumed to be a warning of impending ventricular fibrillation. Further cooling is discontinued immediately and external heat is cautiously applied in order to prevent temperature drift and to encourage rewarming. The ventilation is augmented manually with great care so as not to produce a sudden increase in intrathoracic pressure and consequent decrease in venous return. The inhaled mixture is conveniently altered and its oxygen tension reduced to room air concentration. Up to the present time, in spite of our experimental data, we have not used, nor do we advocate the use of, a straight hypoxic mixture in these cases. Until now, these modifications in the management of clinical hypothermia after the abnormal electrocardiographic wave is observed have not resulted in any instance of ventricular fibrillation or standstill.

SUMMARY

Under the conditions of the experiment it has been possible to produce the appearance of a peculiar wave in the electrocardiogram of hypothermic dogs. This wave is very similar morphologically to a wave which is seen in human beings at comparable hypothermic levels.

A numerical correlation exists between the appearance of this wave and the incidence of ventricular fibrillation, so that the hypothesis that this wave should be considered as a premonitory sign of ventricular fibrillation seems justified.

Hyperventilation does not affect significantly the temperature at which the wave appears, but it increases the margin between this temperature and the temperature at which ventricular fibrillation eventually supervenes.

Possible clinical implications of these findings are discussed.

The author wishes to acknowledge the valuable technical assistance of Miss Margaret M. Riedy throughout the clinical and experimental portions of this work.

REFERENCES

1. Burns, H. L.: Air Surgeons Bulletin **2**:306, 1945.
2. Gunton, R. W., Scott, J. W., Lougheed, W. M., and Botterell, E. H.: Am. Heart J. **52**:419, 1956.
3. Hamilton, J. B., Dresbach, M., and Hamilton, R. S.: Am. J. Physiol. **118**:71, 1937.
4. Hoff, H. E., and Stansfield, H.: Am. Heart J. **38**:193, 1949.
5. Hook, W. E., and Stormont, R. T.: Am. J. Physiol. **133**:334, 1941.
6. Lange, K., Weiner, D., and Gold, M.: Ann. Int. Med. **31**:989, 1949.
7. Ross, D. N.: Guy's Hosp. Rep. **103**:116, 1954.
8. Johannson, B., Biörck, G., Haeger, K., and Sjöstrom, B.: Acta med. scandinav. **155**:257, 1956.
9. Osborne, J. J.: Am. J. Physiol. **175**:389, 1953.
10. Angelakos, E. T., Deutsch, S., and Williams, L.: Circulation Res. **5**:196, 1957.
11. Bigelow, W. G., Mustard, W. T., and Evans, J. G.: J. Thoracic Surg. **28**:463, 1954.
12. Badeer, H.: J. Thoracic Surg. **35**:265, 1958.

Diaphragmatic Juxtacardiac Leads: Their Value in the Study of the Spread of Activation and the QRS Complex of the Heart's Diaphragmatic Surface

Ennio Barbato, M.D., Antonio Carlos Debes, M.D., Fulvio Pileggi, M.D., Toshyasu Fujioka, M.D., Paulo de Paula e Silva, M.D., and Luiz V. Décourt, M.D.
São Paulo, Brazil

It is technically impossible to record any lead in the diaphragmatic surface of the heart during a routine thoracotomy. Actually, the study of the activation's sequence and QRS morphologies in the human epicardial surface has been possible only in the anterior and lateral surfaces of the heart.[1,2] The present paper reports an attempt to obtain information on the diaphragmatic surface of the heart by means of the juxtacardiac diaphragmatic leads during abdominal surgery. These leads have not been reported in the literature.

A study of this type contributes to the problem of the heart's electrical field and also completes the knowledge furnished by direct epicardial leads.

MATERIAL AND METHOD

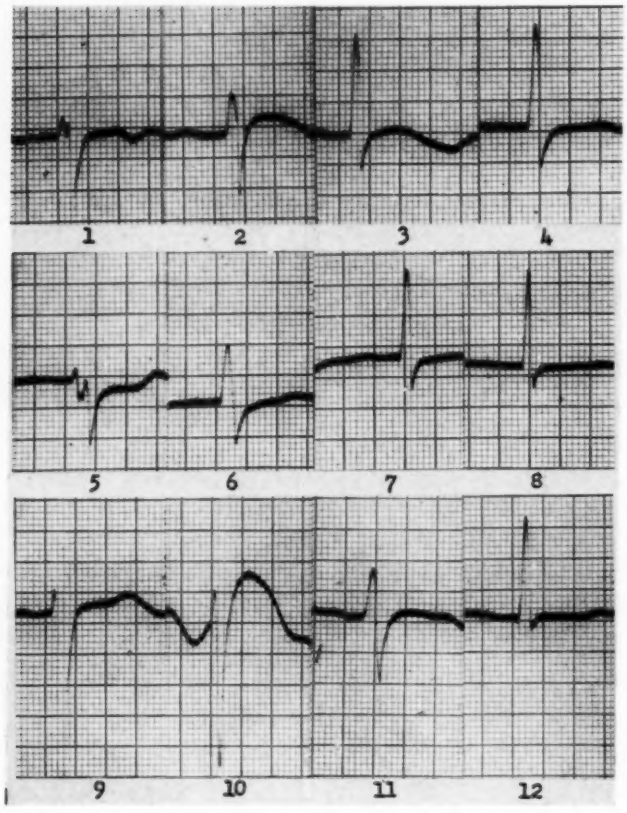
Twelve patients who underwent surgery for gastroduodenal ulcer were studied. Eight had clinically, radiologically, and electrocardiographically normal hearts; two had an S_1-S_2-S_3 electrocardiographic pattern; one had pulmonary emphysema; and one had left ventricular hypertrophy (essential arterial hypertension). Two of the normal patients were women, and all the others were men; their ages ranged from 27 to 50 years, except for the emphysematous patient who was 64 years old.

Multiple thoracic leads with points ranging between 60 and 84 were recorded with a Cambridge "Simpli-Scribe" machine on the day before the operation. With the patients already anesthetized the standard, unipolar, and Wilson's precordial leads were recorded, and just prior to the gastrectomy the unipolar leads (from 12 to 20 points) were recorded on the diaphragm's abdominal surface (cardiac impression).

Beginning at the most anterior level (apical) and ending at the most posterior one (basal), these points were taken in three or more horizontal levels from the right to the left, usually 4 or 5 points at each level. Those points which were localized more to the right were called points of the "right zone" of the cardiac impression, while those which were localized more to the left were called points of the "left zone," and those in the center were called points of the "intermediate zone." In the figures the recorded leads are presented according to their level and position.

Eight cases were recorded at double speed with a four-channel Sanborn Poly-Viso machine, and the other four were recorded with a Cambridge "Simpli-Scribe," at usual speed.

From the Department of Cardiology, Medical School (Hospital das Clínicas), University of São Paulo, São Paulo, Brazil.
Received for publication Nov. 3, 1958.



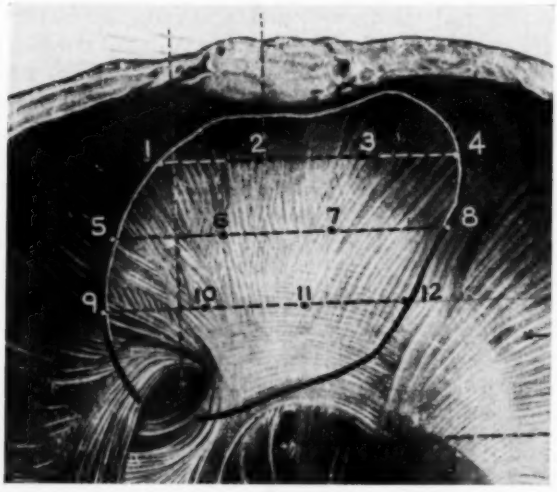


Fig. 1.—M.S., 29 years old, white, male, Italian. *A*, Diaphragmatic juxtacardiac leads obtained at the same points indicated in *B*. *B*, Juxtacardiac diaphragmatic surface. The numbers indicate the points at which leads were recorded.

In order to obtain amplitudes comparable to those in the precordial leads, a maximum of fourfold reduction was necessary. The other details of technique and method are found in previous papers.[1,2]

The multiple thoracic leads were arranged in the figures as though the thorax had been opened at the midline posteriorly and completely extended anteriorly.

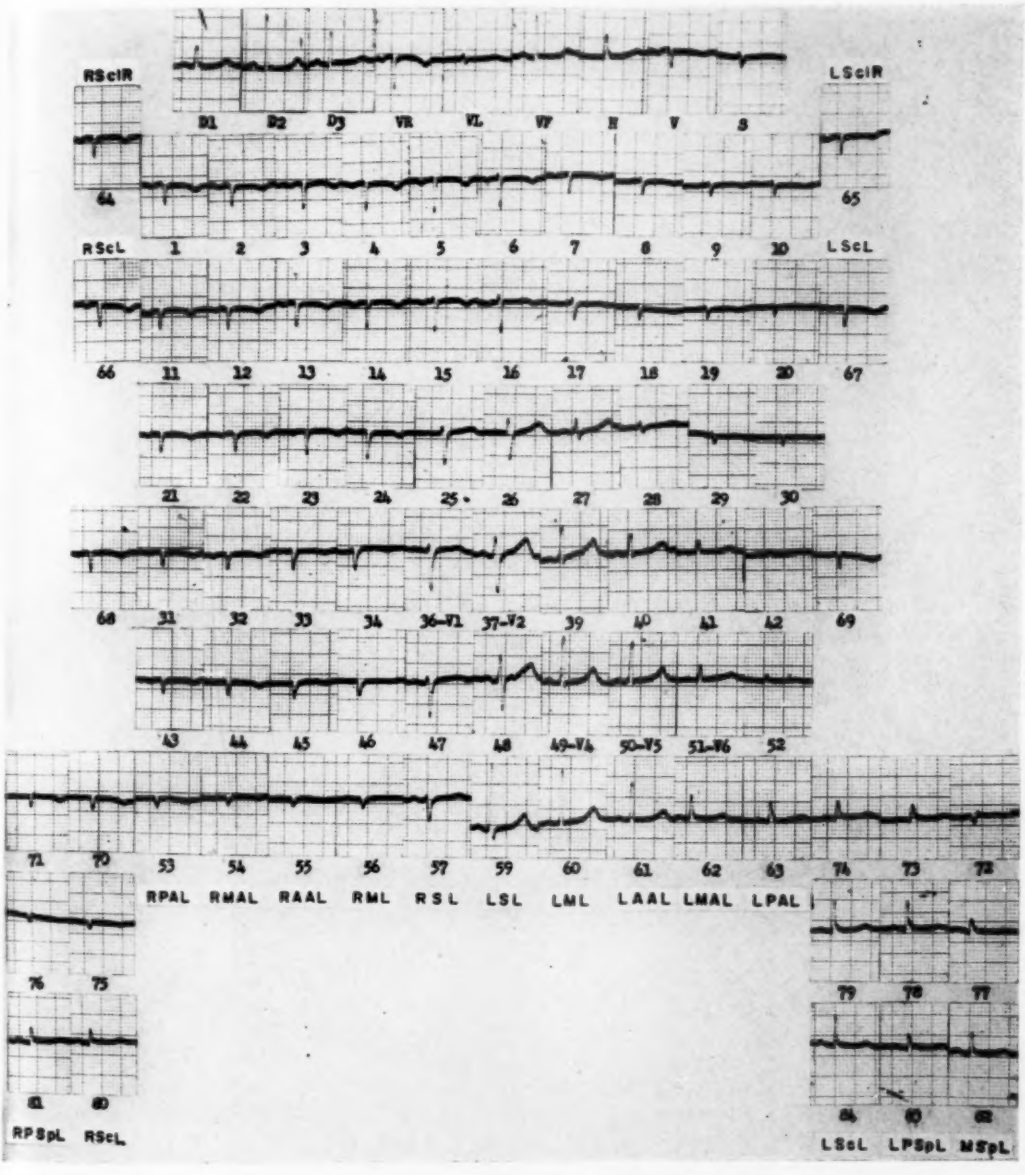
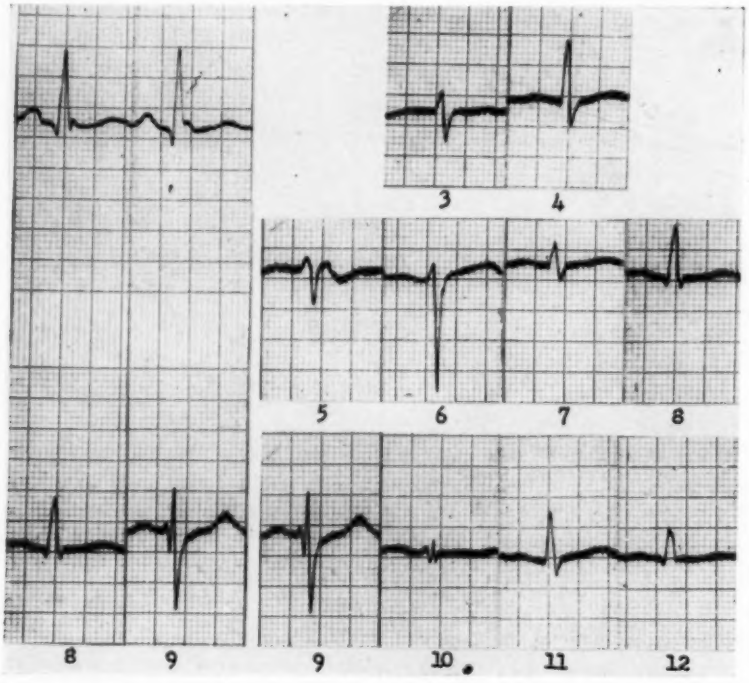


Fig. 1,*C*.—Multiple thoracic leads. The first, second, third, etc., of the horizontal levels correspond, respectively, to the first, second, third, etc., intercostal spaces. *RSclR* = Right supraclavicular region. *LSclR* = Left supraclavicular region. *RPSpL* = Right paraspinal line. *RScL* = Right scapular line. *RPAL* = Right posterior axillary line. *RMAL* = Right mid-axillary line. *RAAL* = Right anterior axillary line. *RML* = Right mammary line. *RSL* = Right sternal line. *LSL* = Left sternal line. *LML* = Left mammary line. *LAAL* = Left anterior axillary line. *LMAL* = Left mid-axillary line. *LPAL* = Left posterior axillary line. *LScL* = Left scapular line. *LPSpL* = Left paraspinal line. *MSpL* = Mid-spinal line.

RESULTS

Figs. 1 and 2 show the recorded pattern obtained in two normal cases. In Tables I and II, corresponding to Figs. 1 and 2, are given the values of the inscription times of the vertices of the deflections and notches. The other six normal cases gave similar patterns and inscription times.



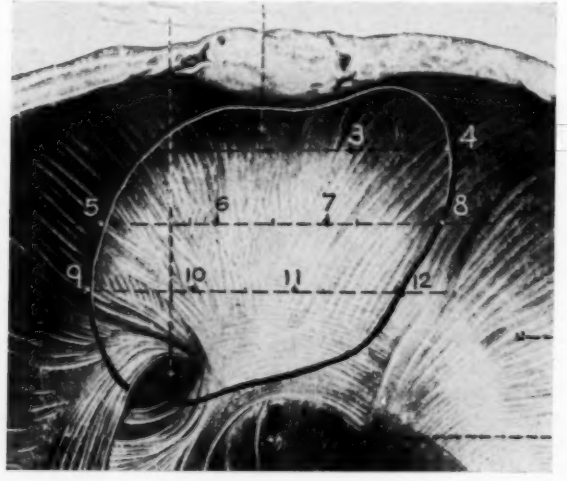


Fig. 2.—J.C.S., 27 years old, white, male, Brazilian. *A*, Diaphragmatic juxtacardiac leads obtained at the same points indicated in *B*. The leads obtained at Points 8 and 9 are repeated together with Lead II, recorded simultaneously. *B*, Juxtacardiac diaphragmatic surface. The numbers indicate the points at which leads were recorded.

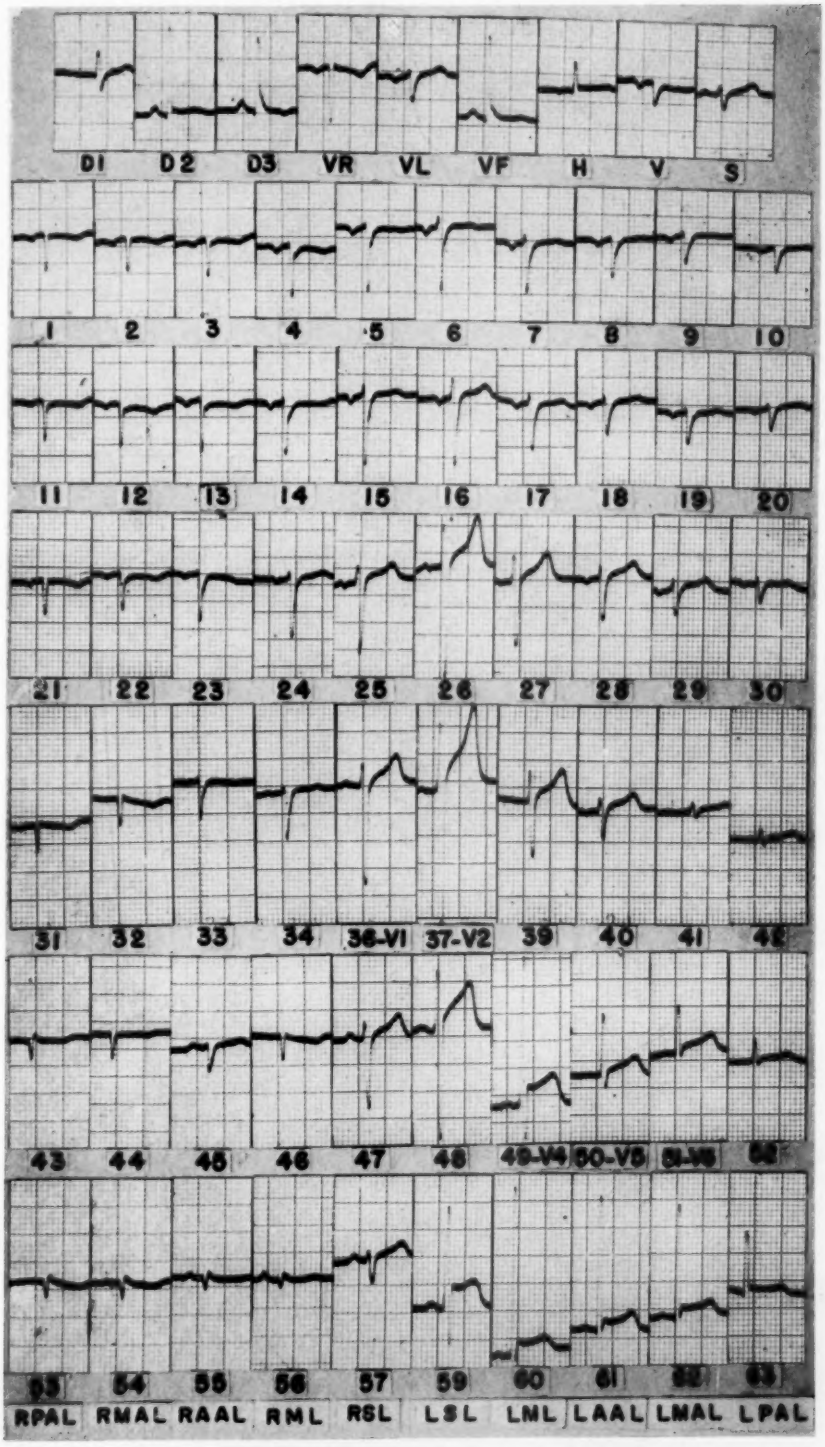


Fig. 2,*C*.—Multiple thoracic leads. The first, second, third, etc., of the horizontal levels correspond, respectively, to the first, second, third, etc., intercostal spaces. *RPAL* = Right posterior axillary line. *RMAL* = Right mid-axillary line. *RAAL* = Right anterior axillary line. *RML* = Right mammary line. *RSL* = Right sternal line. *LSL* = Left sternal line. *LML* = Left mammary line. *LAAL* = Left anterior axillary line. *LMAL* = Left mid-axillary line. *LPAL* = Left posterior axillary line.

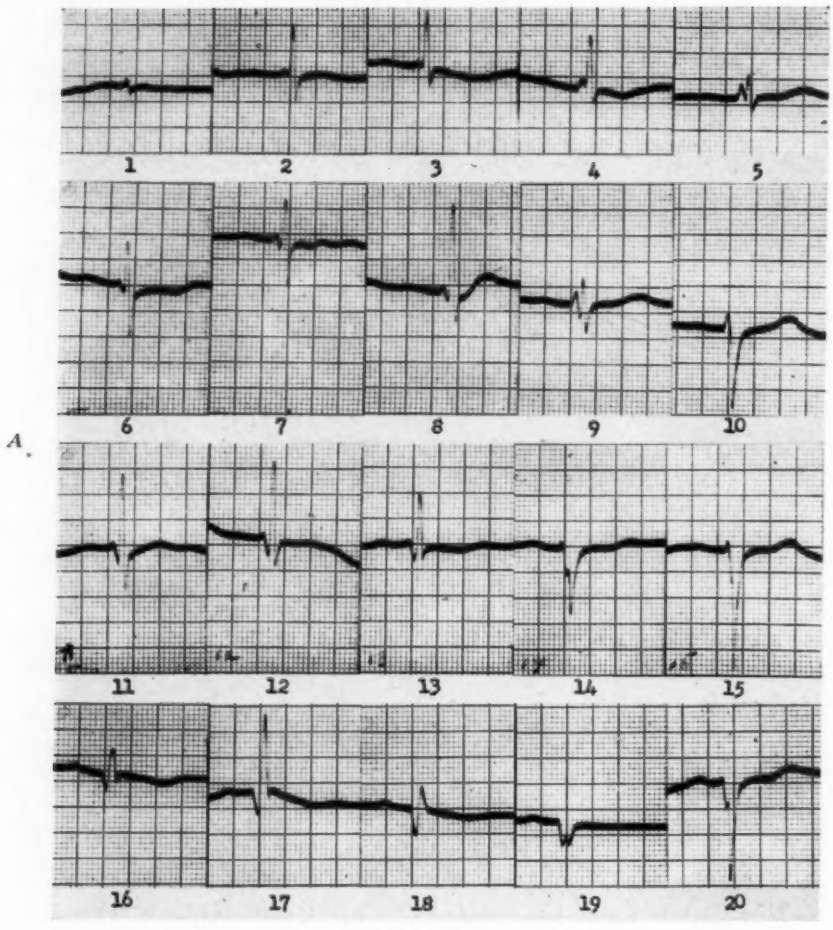
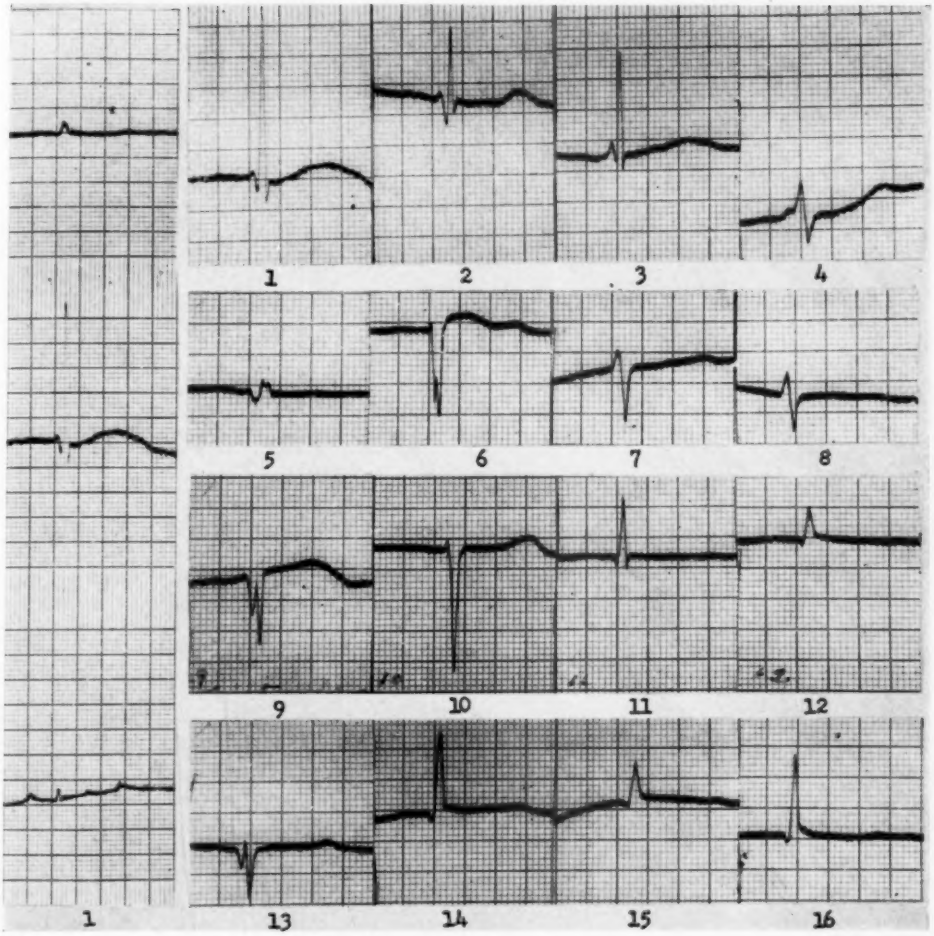
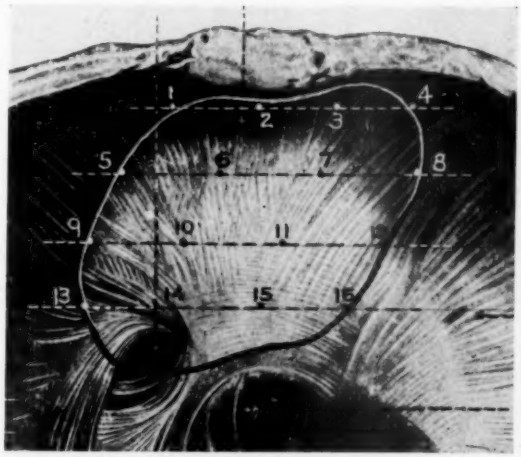


Fig. 3.—F.M., 52 years old, white, male, Brazilian. *A*, Diaphragmatic juxtacardiac leads obtained at the same points indicated in *B*. *B*, Juxtacardiac diaphragmatic surface. The numbers indicate the points at which leads were recorded.



A.



B.

Fig. 4.—J.F., 64 years old, white, male, German. *A*, Diaphragmatic juxtacardiac leads obtained at the same points indicated in *B*. The lead obtained at Point 1 is repeated together with Leads I and II, recorded simultaneously. *B*, Juxtacardiac diaphragmatic surface. The numbers indicate the points at which leads were recorded.

Figs. 3 and 4 show, respectively, the records obtained in one of the cases with an S_1-S_2-S_3 pattern, and in the case of pulmonary emphysema. The case of left ventricular hypertrophy differs from the normal cases only in the larger amplitude obtained in the leads located in the cardiac impression's left zone.

DISCUSSION

In both normal and left ventricular hypertrophy cases, with only one exception, the QRS morphologies in the points of the "left zone" were qRs, qRS, qR, or Rs, that is, there were always tall R waves usually preceded by a Q and followed by an S of variable depth. The points showing no Q waves were usually located in the apex. In the "right zone" the morphologies obtained were: rrS, rsr′S′, rSr′, rsR′S′, RS, rS, and in a single case, Q (r) S. Between both zones the morphologies were rS, RS, qRS, and qRs, the former two nearer the right zone and the latter two nearer the left zone.

As in the diaphragmatic surface the points of the left zone correspond to the left ventricle. One notes that in the left ventricular diaphragmatic surface QRS complexes without Q waves are recorded, contrary to the findings on the anterior and lateral surfaces.[1,2] In the right ventricular diaphragmatic surface QRS complexes with delayed R waves are recorded more frequently than in the right anterior surface. These delayed R waves suggest a later activation of certain regions of the right ventricle, such as the basal and posterior portions. These regions should contribute to the beginning of the final right and backward dislocation of the vectorcardiographic loop.

The recorded morphologies on the diaphragmatic surface near the left border of the cardiac impression are very similar to those recorded at the fourth, fifth, sixth, seventh, and eighth left intercostal spaces lateral to the mid-clavicular line (Figs. 1 and 2), to those at the inferior level of the left bronchus,[5,8,12] and to some of those from the esophagus.[3,9,10,11] The morphologies recorded on the right border of the cardiac impression, with broad double R and S, are not found, however, on the chest surface, in the esophagus, in the bronchus, or in the limbs, and they were not even referred to in the infradiaphragmatic regions by Helm and associates.[6] The reason for these facts deserves further attention. The rSr′ is the only pattern that might be recorded in the upper intercostal spaces of the right hemithorax.

In the cases of the S_1-S_2-S_3 pattern (Fig. 3) the predominant morphology in the right and intermediate zones of the diaphragmatic surface is double R and S. This strengthens the findings of Grant[4] and ourselves,[2] according to which in a certain number of patients with such an electrocardiographic pattern, its genesis is due to an uncommon and peculiar activation and not to a special position of the heart.

In the case of pulmonary emphysema the morphology as well the amplitude is similar to those of the normal. The great decrease in the amplitude (Fig. 4) which is observed in the peripheral and thoracic leads is due, therefore, to the spread of the electrical forces through the lungs.

The spread of activation in the diaphragmatic surface is from the paraseptal zones to both sides, and from the apex to the base, just as it is in the anterior and lateral surfaces. If one compares the activation times of the different points on the diaphragmatic surface (Tables I and II) and those of the other two surfaces,[2] it becomes obvious that the sequence of the activation of the heart, in the majority of the cases, is as follows: septum, right paraseptal zone, and some areas of the left paraseptal zone, remnant of the left paraseptal zone, apex of both ventricles, intermediate zones of both surfaces of the right ventricle, and pulmonary conus; next, the intermediate zone of the left ventricle and basal zone of the right ventricular anterior surface, followed immediately by the

TABLE I

	POINT	MORPHOLOGY	Q (SEC.)	R (SEC.)	S (SEC.)	Q/R/S	I.I.T. (SEC.)
First Level	1	r (r) S		0.024–0.034	0.052	2.6/30	0
	2	rS		0.028	0.056	6.2/11.2	0.010
	3	Rs		0.034	0.054	15.6/5.0	0.012
	4	Rs		0.046	0.064	15.8/5.0	0.020
Second Level	5	r (sr) S		0.022	0.040–0.072	1.5/10	0.020
	6	Rs		0.042	0.068	8.5/5.0	0.016
	7	qRs	0.06	0.048	0.072	0.2/13.7/3.7	0.020
	8	qRs	0.06	0.048	0.060	0.3/14.8/2.51	0.020
Third Level	9	rS		0.014	0.038	0.2/3.4/35.2	0.002
	10	rS		0.022	0.042	5.7/29.5	0.014
	11	RS		0.040	0.066	7.2/9.8	0.012
	12	qRs	0.08	0.046	0.066	15.8/1.5	0.020

I.I.T. = Initial inscription time.

TABLE II

	POINT	MORPHOLOGY		R		S	AMPLITUDE	I.I.T.
First Level	3	qRS	?	0.030		0.044	3.0/4.7	0.004
	4	qRs	?	?		?	9.7/3.8	?
				R		S		
Second Level	5	rSr′(?)		0.032		0.052	1.5/6.3/?	0.006
	6	rS		0.022		0.038	2.4/18.4	0.000
			Q	R		S		
	7	qRS	0.012	0.034		0.052	0.3/3.4/2.1	0.012
	8	qRs	0.014	0.036		0.058	1/8.0/1.4	0.004
			R	S	R′	S′		
Third Level	9	rsR′S′	0.012	0.024	0.036	0.046	1/4/6.5/14.5	0.004
	10	rSR′s′	0.012	0.030	0.044	0.050	?/?/5/4	0.010
			Q	R		S		
	11	qRs	?	0.032		0.056	0.5/7.5/3	0.014
	12	qRs	0.016	0.036		0.062	1/4.5/0.3	0.008

basal zones of the left ventricle; and finally, the basal zones of the right ventricle near the right border and the upper portions of the left ventricle. In some other cases the pulmonary conus is activated very early.

The inscription times of the vertices of various deflections in the diaphragmatic leads (Tables I and II) show a tendency to a greater synchronism than do those recorded in the epicardial surface, and a lesser synchronism than do those in the thoracic and limb leads. The amplitude of the diaphragmatic leads is shorter than that obtained on the epicardial leads. Both facts probably mean that the diaphragmatic leads are in an intermediate position between the epicardial and the thoracic leads; that is, they behave as if they were nearer to the heart than are the thoracic leads.

The P wave, when sharply inscribed, is positive in every point. The T wave is always positive except in a few points near the right border of the cardiac impression, where it is negative.

SUMMARY

In 12 patients who underwent gastric surgery, juxtacardiac diaphragmatic leads were recorded. In normal patients the recorded morphologies were: qRs, qRS, qR, and Rs in the left lateral portion of the cardiac impression of the diaphragm, and rS or double R and S in the right lateral portion. Thus, complexes without Q waves are recorded in zones corresponding to the left ventricle. This is not observed in the anterior and lateral surfaces of this ventricle.

It is suggested that the diaphragmatic surface of the right ventricle, through its basal portions near the right border, interferes directly in the genesis of the delayed R waves of the RSR′ and RSR′S complexes.

By the study of the S_1-S_2-S_3 pattern it was concluded that even in normal people this pattern is due to a special and uncommon type of ventricular activation.

The data obtained in this study was related to data obtained previously with the direct epicardial leads, in an attempt to complete our knowledge of the sequence of cardiac activation.

In both normal and pathologic cases the P wave is always positive. The T wave, except in few points near the right border of the heart, is always positive.

REFERENCES

1. Barbato, E.: Estudo eletrocardiográfico de ativação ventricular normal e patológica, Tese, Fac. de Medicina de São Paulo, 1952.
2. Barbato, E., Pileggi, F., Debes, A. C., Fujioka, T., Tranchesi, J., San Juan, E., Magalhães, M.S., and Décourt, L. V.: Am. Heart J. **55**:867, 1958.
3. Brown, W. E.: Am. Heart J. **12**:1, 1936; **12**:307, 1936.
4. Grant, R. P.: Circulation **2**:676, 1950.
5. Goldstein, J., Pordy L., Chesky, K., Arai, H. S., Snyder, E. R., and Fenerstein, S.: Circulation **3**:911, 1951.
6. Helm, J. D., Helm, G. H., and Wolferth, C. C.: Am. Heart J. **27**:755, 1944.
7. Kossmann, C. E., Berger, A. R., Rader, B., Brumlik, J., Briller, S. A., and Donnelly, J. K.: Circulation **2**:10, 1950.
8. Langner, P. H., and Atkins, J. P.: Circulation **2**:419, 1950.
9. Mena, S. A.: Rev. cubana de cardiol. **7**:73, 1946.
10. Scherlis, L., Wener, J., Grishman, A., and Sandberg, H.: Am. Heart J. **41**:246, 1951.
11. Schlesinger, P., Benchimol, A. B., and Cotrim, M. R.: Am. Heart J. **37**:1110, 1949.
12. Zuckermann, R., Bisteni, A., Ortiz, J., and Rodriguez, M. I.: Arch. Inst. cardiol. México **20**:387, 1950.

Myocardial Infarct-Like Lesions and Arteriosclerosis Induced by High Molecular Substances, and Prevention by Magnesium Salt

T. Shimamoto, M.D., T. Fujita, M.D.,* H. Shimura, M.D.,* H. Yamazaki, M.D.,* S. Iwahara, M.D.,** and G. Yajima, M.D.,*** Tokyo, Japan*

In 1957, the authors[1] reported a method that would regularly induce large myocardial infarct-like lesions in rabbits and rats, fed either on a low- or high-fat diet, using polysaccharide of gram-negative bacteria and a combination of adrenaline and noradrenaline. In this experiment it was emphasized that the animals, treated with bacterial polysaccharide and adrenaline, showed not only large myocardial lesions with calcification, but also a remarkable elastofibrous thickening of the intima of the coronary arteries, especially those located in the myocardium of the left ventricle. The intimal thickening due to fibrosis was apparent also in the aorta, and an increase of metachromatic substance in the intimal layer and fragmentation of the internal elastic membrane were found, aside from the appearance of arteriosclerosis of the Mönckeberg type. Such a change in the intima of the artery showed a definite contrast when compared with the simple Mönckeberg's medial necrosis of the animals treated with adrenaline or noradrenaline alone.

Upon the systematic exploration of the biological effect of polysaccharide it was found recently by the authors[2-5] that polysaccharide induces precipitation of fibrinogen, clumping of platelets and leukocytes, and shortening of the whole-blood coagulation. Also, the appearance of platelet-agglutinating substance and a small amount of serotonin were found in the plasma after the administration of the polysaccharide to rabbits.

According to the research of Landy and Shear,[6] such a property of bacterial polysaccharide seems to be a common feature of the various high molecular substances, not only those of bacterial origin but also those from various animal tissues and plants, including liver glycogen, dextran, kaolin, and the antigen-antibody precipitates which were described earlier by Stetson[7] and Walton.[8]

This work was supported by a grant from the Japanese Ministry of Education.
Received for publication Sept. 10, 1958.
*Department of Clinical Physiology, Tokyo Medical and Dental University, Tokyo, Japan.
**Department of Bacteriology, National Hygienic Laboratory, Tokyo, Japan.
***Department of Pathology, Tokyo Medical and Dental University, Tokyo, Japan.

TABLE I. MICROSCOPICAL FINDINGS ON RABBITS‡

TREATMENT	RABBIT NUMBER	HEART									AORTA		OTHER ORGANS	
		MYOCARDIUM			CORONARY ARTERY									
					MAIN STEM		SMALL OR MEDIUM-SIZED ARTERY		ARTERIOLE					
		SCAR	FIBROSIS	DEGENERATION	INTIMA*	MEDIA**	INTIMA*	MEDIA**	INTIMA*	MEDIA**	THICKENING OF INTIMA	CHANGE OF MEDIA***	CHANGE OF PARENCHYMA	CHANGE OF ARTERY****
Polysaccharide (50 μg/Kg.) Adrenaline (10 μg/Kg.)	84	+	+++	+++	±	+	++	+	+	+	+	±	−	+
	85	−	+++	++	−	±	+	+	+	+	−	±	−	+
	86	+	+++	+++	+	+	+++	+	+	++	+	±	−	+
	87	++	+++	+++	±	±	++	+	+	+	−†	±	−	+
	88	+	+++	+++	+	+	+++	+	+	++	+	±	−	+
	96	+	++	+++	±	±	++	+	+	+	+	+	−	+
$MgCl_2$ (3 Gm./day) Polysaccharide (50 μg/Kg.) Adrenaline (10 μg/Kg.)	79	−	+	+	−	−	+	±	±	+	+	±	−	±
	81	−	+	+	−	−	++	+	+	+	−	−	−	±
	83	+	++	+++	−	±	+	±	±	+	−	−	−	±
	94	−	±	+	±	−	+	±	±	±	−†	±	−	±
	97	−	+	+	±	±	++	±	±	+	−	−	−	±
	98	−	+	±	−	−	+	±	±	±	−	−	−	±

Polysaccharide (50 μg/Kg.)	111	+	++	++	−	+	±	+	−	−	−	±	±
	112	+	++	++	−	++	+	+	−	−	−	±	±
	113	−	+	+	−	+	−	±	−	−	±	±	±
	114	−	+	+	−	±	−	±	−	+	±	±	±
	115	−	+	+	−	±	−	±	−	−†	±	±	±
Adrenaline (10 μg/Kg.)	65	−	±	±	−	±	−	±	−	−	−	−	−
	72	−	±	−	−	±	−	−	−	−	−	−	−
	73	−	±	±	−	±	−	−	−	−	−	−	−
	89	−	−	−	−	±	−	±	−	−	−	−	−
	90	−	−	−	−	±	−	±	−	−	−	−	−
No Treatment	22	−	−	−	−	−	−	−	−	±	−	−	−
	25	−	−	−	−	−	−	−	−	−	−	−	−
	30	−	−	−	−	−	−	−	−	−	−	−	−
	33	−	−	−	−	−	−	−	−	−	−	−	−
	54	−	−	−	−	−	−	−	−	−	−	−	−
	55	−	−	−	−	−	−	−	−	−	−	−	−
	56	−	−	−	−	−	−	−	−	−	−	−	−

‡This table shows the pathologic findings of the animals sacrificed 5 weeks after the initiation of treatment. However, the following animals were sacrificed earlier: Group IV (No. 96 after 2 weeks, No. 84 and 86 after 4 weeks); Group V (No. 81 and No. 98 after 4 weeks); Group III (No. 112 after 2 weeks); Group II (No. 90 after 3 weeks).

*Fibrosis or elastofibrosis.

**Slight muscle-fiber degeneration accompanied by histolytic edema of the interstitium.

***Slight fibrosis or degenerative change of the elastic fibers (irregularity or fragmentation with or without swelling).

****Fibrous thickening of the intima with or without slight medial degeneration.

†Swelling of the endothelial cells.

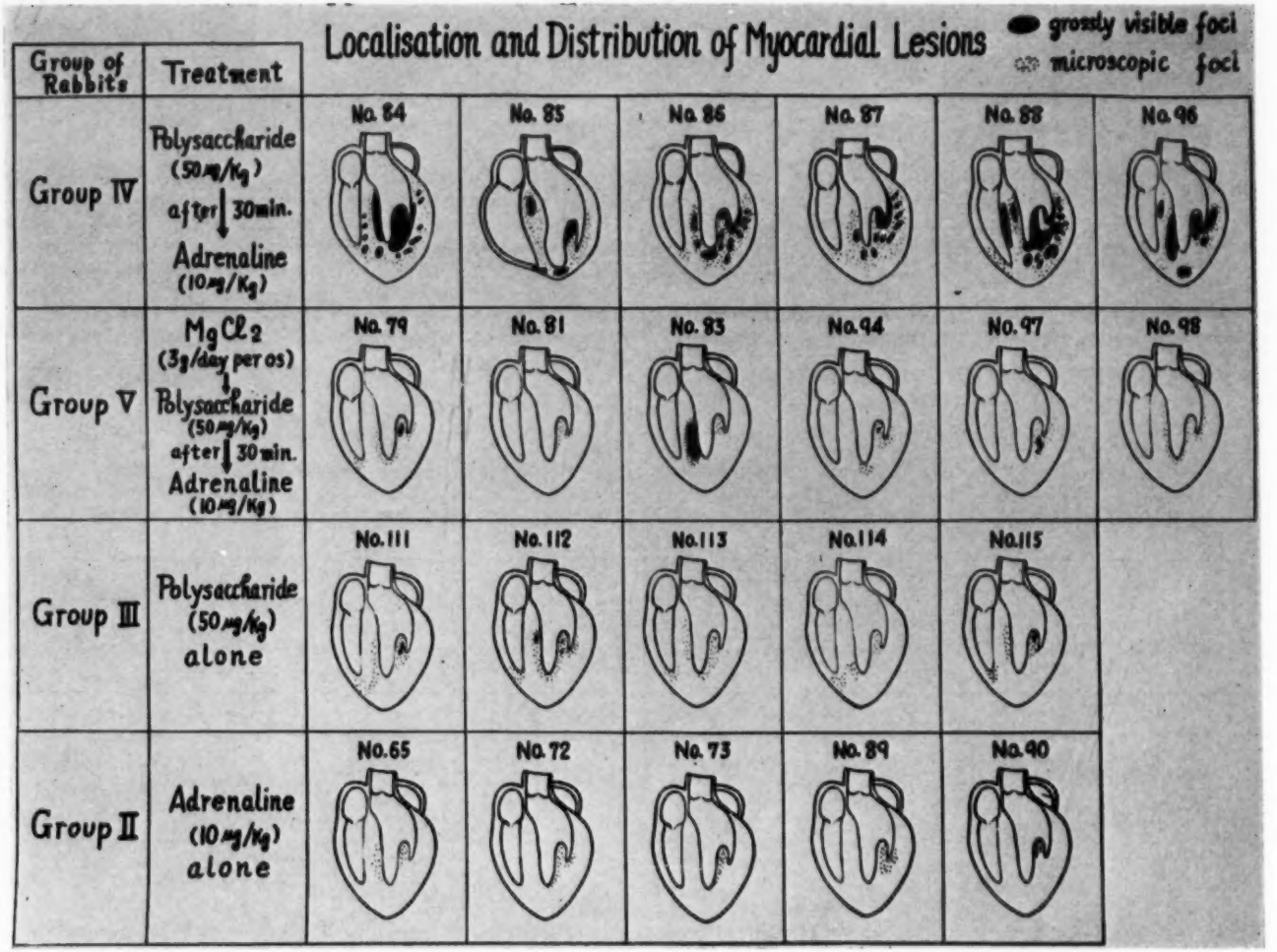


Fig. 1.—This figure shows the localization and the distribution of the myocardial lesions of the animals sacrificed within 5 weeks after the initiation of the treatment, comparing the difference in lesions among the four groups of animals.

These high molecular substances have properties which cause an intravascular coagulation of the blood and are capable of eliciting the Shwartzman reaction. When a sufficient dose of these substances was injected intravenously, the succeeding intradermal injection of adrenaline caused local hemorrhagic necrosis, as shown by Thomas and associates,[9] by Landy and Shear,[6] and also by the authors.[10] In the authors' experiment employing electron microscopy[11] it was found that the intradermal administration of adrenaline seemed to promote the adherence of the following substances to the endothelial cells of the capillaries; that is, the electrodense plasma substance and platelet-leukocyte thrombi which appeared in the circulating blood were mobilized from the blood by the high molecular substance, as in the case of the generalized Shwartzman reaction of Pappas, Ross and Thomas.[12] Thus, the occlusion of capillaries is induced and results in local hemorrhage.

On the basis of such a finding the authors changed the mode of administration of both substances in the following way in this experiment. First, the dosage of the polysaccharide was increased twice, i.e., from 25 to 50 μg per kilogram of animal body weight, and it was ascertained that this would cause a definite precipitation of fibrinogen and clumping of platelets and leukocytes. On the contrary, the dosage of adrenaline was reduced from 25 μg to 3 to 10 μg per kilogram of animal body weight. Secondly, the administration of the polysaccharide was performed 30 minutes before the administration of adrenaline whenever they were used together; that is, after sufficient development of clumping of platelets and a possible precipitation of fibrinogen in the circulating plasma by pretreatment with polysaccharide following the administration of adrenaline, which might induce a stimulation of the metabolism of heart and blood vessels, and which, presumably, as the consequence, might change the quality of the endothelial cells of the blood vessels so as to cause these substances to adhere to the endothelium, as shown electron-microscopically by the authors and reported elsewhere.[11]

It is the object of this communication to report on the experiments on rabbits which show: (1) that the repetitious administration of a sufficient dosage of bacterial polysaccharide, which is capable of precipitating fibrinogen and clumping platelets, induced the damage to the artery, especially of the intimal layer, and the myocardial infarct-like lesion; (2) that the combined use of adrenaline and bacterial polysaccharide induced remarkably exaggerated damage to the heart and the artery without the appearance of Mönckeberg's medial necrosis; and (3) that the concurrent administration of magnesium chloride showed some preventive effect against this damage to the heart and artery.

MATERIALS AND METHODS

Thirty-four male rabbits were fed on the ordinary, low-fat diet of barley corn and vegetables of the authors' laboratory, and were divided into 5 groups.

The first group of animals was the control. The second group received 10 μg of adrenaline per Kg. of body weight, intravenously, every 2 days for 4 weeks. The third group received 50 μg of polysaccharide per Kg. of body weight, intravenously, every 2 days for 4 weeks. The fourth group received 10 μg of adrenaline per Kg. of body weight, intravenously, 30 minutes after the intravenous pretreatment with 50 μg of polysaccharide per Kg. of body weight, for 2 to 4 weeks.

In 2 animals, 3 instead of 10 μg of adrenaline per Kg. of body weight was also utilized. The fifth group received 50 μg of the polysaccharide, followed by 10 μg of adrenaline, per Kg. of body weight, as in the animals of the fourth group, and at the same time they received an oral administration of 1.5 Gm. of $MgCl_2 \cdot 6H_2O$ twice daily for 5 weeks.

Treatment with $MgCl_2$ was begun 3 days prior to initiating the administration of polysaccharide and adrenaline, in order first to permit some degree of adaptation to this salt. It was very well tolerated.

Bacterial Polysaccharide.—Bacterial polysaccharide was prepared from *Shigella flexneri 2b*, strain K3. The bacteria were cultured on the nutrient agar plate and the harvested cells were dried with acetone. The endotoxin was extracted from the dried bacteria, using 90 per cent phenol, followed by precipitation with ethanol. The precipitate was dried and purified by acetone fractionation as well as by starch zone electrophoresis. Thus, a purified endotoxin was prepared. The purified endotoxin was then dissolved with 1 per cent acetic acid and was hydrolyzed for

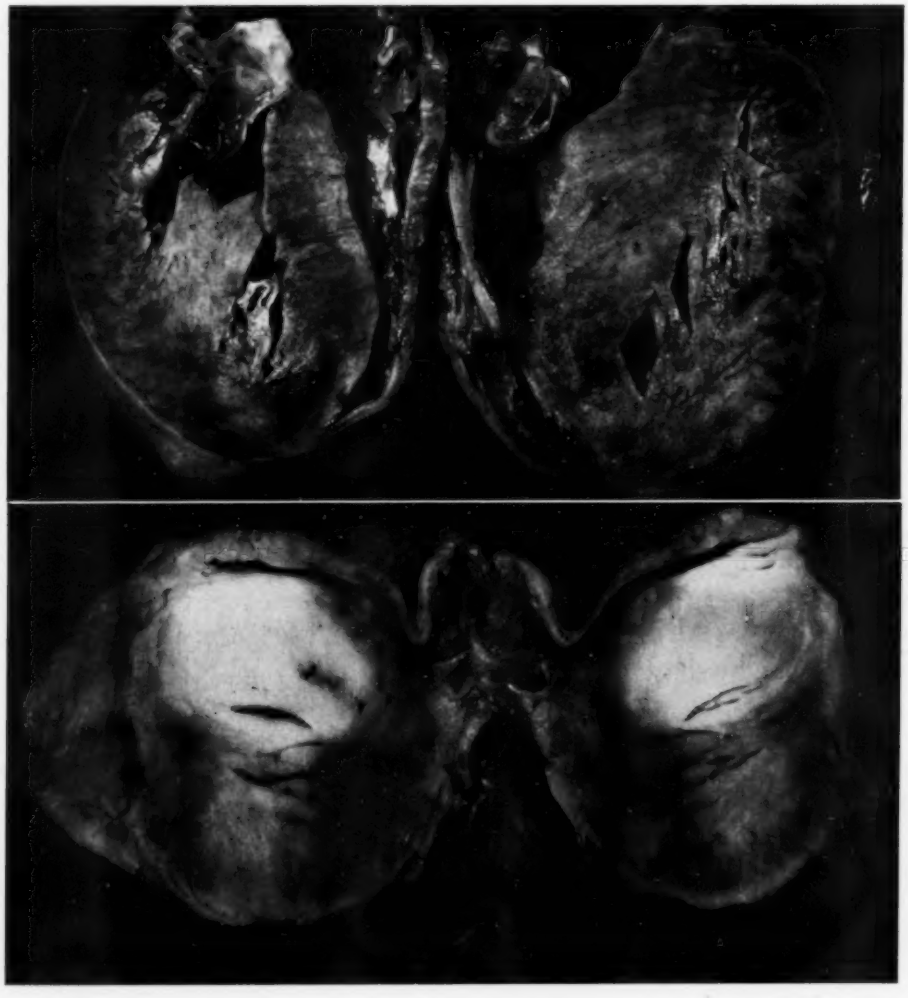


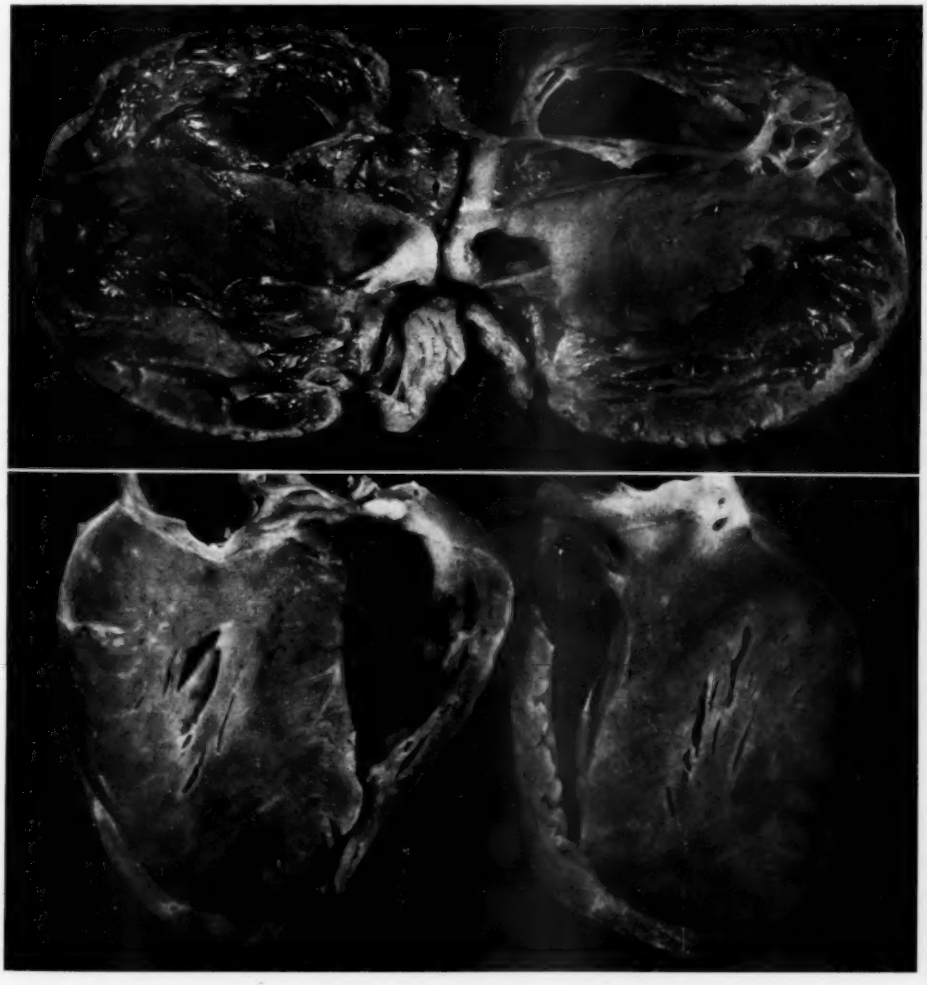
Fig. 2,*A*.—Top: Cut surface of the heart of rabbit No. 88, which received 12 injections of bacterial polysaccharide (50 μg/Kg.) and adrenaline (10 μg/Kg.) within 5 weeks. Several grayish-white, cloudy foci can be seen in various parts of the heart, with congestive portions of irregular black stripes. Bottom: Transmural myocardial infarct in the anterior wall of the left ventricle of rabbit No. 117, which received 12 injections of the bacterial polysaccharide (50 μg/Kg.) and adrenaline (3 μg/Kg.) in the course of 4 weeks.

4 hours at 100° C., and from the supernatant of the hydrolyzate the polysaccharide fraction was prepared. The polysaccharide was freshly dissolved with physiologic saline to contain 200 μg to 1 c.c. in each experiment, and was administered into the vein of the ear.

Adrenaline.—Adrenaline Sankyo was freshly dissolved in physiologic saline to contain 40 μg in 1 c.c. in each experiment, and was injected into the vein of the ear of the rabbits.

The experiment was terminated by killing all surviving rabbits by air embolism at the end of 5 weeks. Among the animals of Group IV, treated with both polysaccharide and adrenaline, 3 were sacrificed earlier, i.e., 4 weeks after the initiation of injection, because they began to be somewhat disinclined to feed; they were sacrificed immediately and one animal died 2 weeks after the initiation of the treatment from perforating ulcer of the stomach. Four were kept alive for 5 weeks, and 5 for 12 weeks, and then all were sacrificed.

Immediately after autopsy, the whole internal organs were fixed in neutral formalin and Carnoy's fixative for subsequent histochemical demonstration. Each organ was weighed and observed macroscopically, and the ordinary pathologic exploration was carried out, using hema-



B.

C.

Fig. 2,*B.*—Marked aneurysmatic dilatation of the apical parts of both ventricles due to myocardial necrosis in rabbit No. 85, which received 12 injections of bacterial polysaccharide (50 μg/Kg.) and adrenaline (10 μg/Kg.) within 5 weeks. *C*, Cut surface of the heart of rabbit No. 79, which received 12 injections of the bacterial polysaccharide (50 μg/Kg.) and adrenaline (10 μg/Kg.) within 5 weeks, with concurrent administration of $MgCl_2 \cdot 6H_2O$ (3 Gm./day), showing normal appearance.

toxylin and eosin, elastica-van-Gieson, toluidine blue, and Altmann-Kull's mitochondrial stain. Altmann-Kull's technique was found to be a very suitable method for determining the small coagulative degeneration of the myofiber of the myocardium. To demonstrate calcium, von Kossa's silver nitrate technique was applied on the slide, slightly counterstained with hematoxylin and eosin, and in order to demonstrate fat deposition, Sudan III stain was also applied.

The biological effect of the polysaccharide used in this experiment was tested for its effect on the blood. In rabbits it was revealed that the intravenous administration of 50 μg of the polysaccharide induced a −35 to −70 per cent decrease in circulating platelets, from 30 minutes to 2 hours after the administration, with recovery within 4 to 48 hours; it also induced a −25 to −60 per cent decrease in circulating leukocytes, chiefly granulocytes, simultaneously with the decrease in platelets, with recovery after 1 to 4 hours and an increase, and then a leukocytosis of 12,000 to 15,000 per cubic millimeters was observed 2 to 4 hours after the administration. The erythrocytes showed a slight increase (+10 to +20 per cent) 30 minutes after the injection of polysaccharide, and then recovered 2 to 4 hours after.

According to the electron microscopical investigation[11] the administration of 50 μg of the polysaccharide caused swelling of the endothelial cells of the capillaries and arteries of the myocardium and the appearance of platelet-leukocyte thrombi with electrodense plasma substance adhering to them. The subsequent administration of 10 μg of adrenaline per Kg. of body weight promoted the changes.

Pyrogenicity of the polysaccharide was minimal. The intravenous administration of 50 μg of the polysaccharide per Kg. of body weight caused a slight elevation, 0 to 0.7° C., in the rectal temperature of the rabbits in the course of 1 to 3 hours after the administration.

Adrenaline-Sensitizing Effect of the Polysaccharide Preparation.—The intradermal injection of 10 μg of adrenaline in 0.1 c.c. of saline, which was performed within 4 hours after the intravenous injection of 50 μg of the polysaccharide per Kg. of body weight, induced hemorrhagic necrosis.

Lethal Dose of the Polysaccharide Preparation.—Into 6 rabbits, 3,000 μg per Kg. of body weight of this preparation, and into 3 rabbits, 5,000 μg per Kg. of this preparation, were injected as a single shot; all survived.

After the oral administration of $MgCl_2$ as described above, the administration of polysaccharide, 50 μg per Kg. of animal body weight, with or without the succeeding adrenaline administration, inhibited strikingly the effect of decreasing circulating platelets and leukocytes.

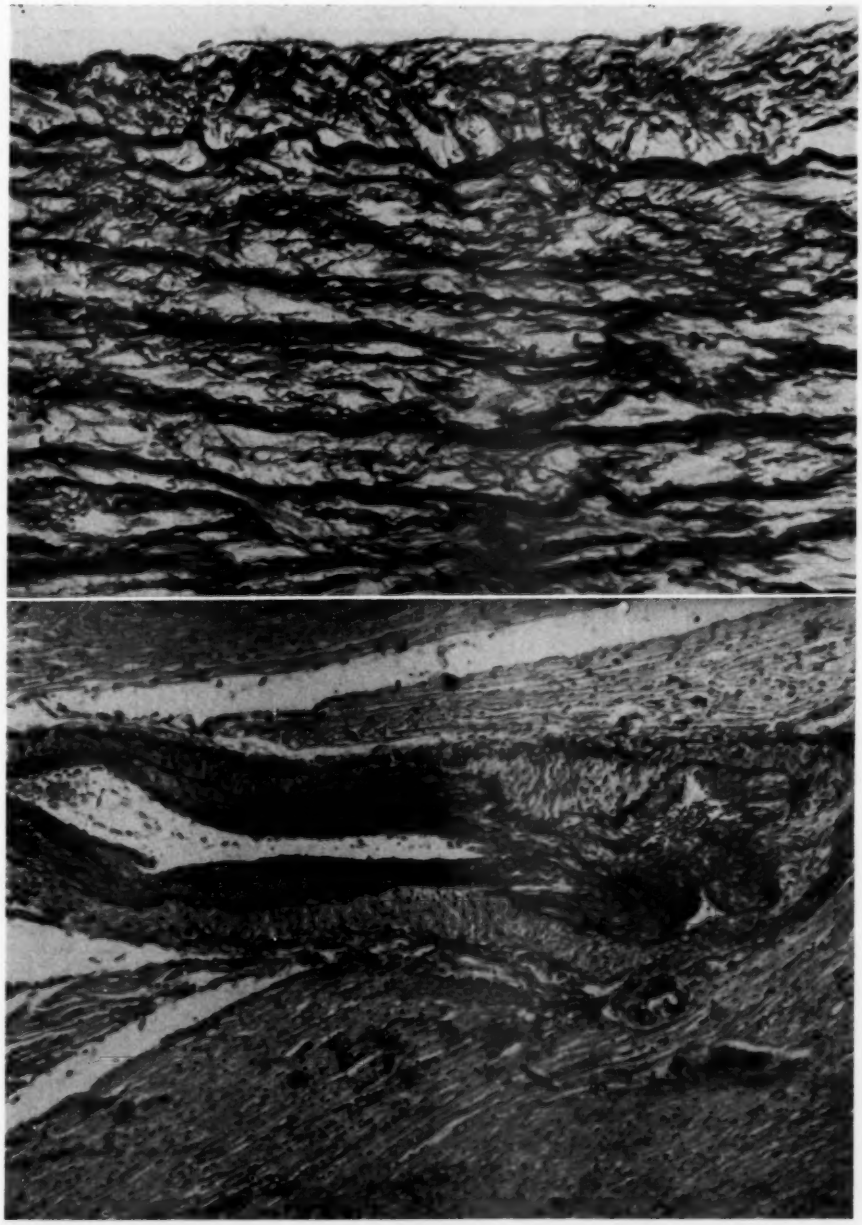
RESULTS

1. Control rabbits showed no lesions on gross and microscopical examinations of the artery and heart.

2. As seen in Table I, animals treated with adrenaline alone showed no change indicating Mönckeberg's sclerosis in the aorta. And in the heart there was no visible change except for a very few scattered coagulative necrotic foci of myofiber and fibrosis, shown by Altmann-Kull's mitochondrial stain, which are scarcely recognizable microscopically.

3. Animals treated with polysaccharide alone showed a slight change in the intima of the aorta in 2 of 5 animals, revealing a slight subendothelial fibroblastic proliferation and swelling of the endothelial cells. In 3 of 5 animals a slight irregularity of the muscle fiber of the media was observed, and in 1 animal there was a slight edema. In all animals the elastofibrous thickening of the intima mentioned above was found in some of the medium-sized and small coronary arteries. In 3 of 5 the change was a little stronger, showing a subendothelial fibroblastic proliferation, deposition of metachromatic substance, and fragmentation of internal elastic membrane. In all 5 animals a slight thickening of the intima was also observed in some of the medium-sized arteries of the lung.

In the heart there were small visible infarct-like lesions in the papillar muscle of the left ventricle in 3 of 5 rabbits, and in all rabbits there were microscopically observable small, degenerative, and fibrotic foci scattered in the myocardium of the left ventricle, as shown in Fig. 1. In 2 of the 5 animals a microscopically

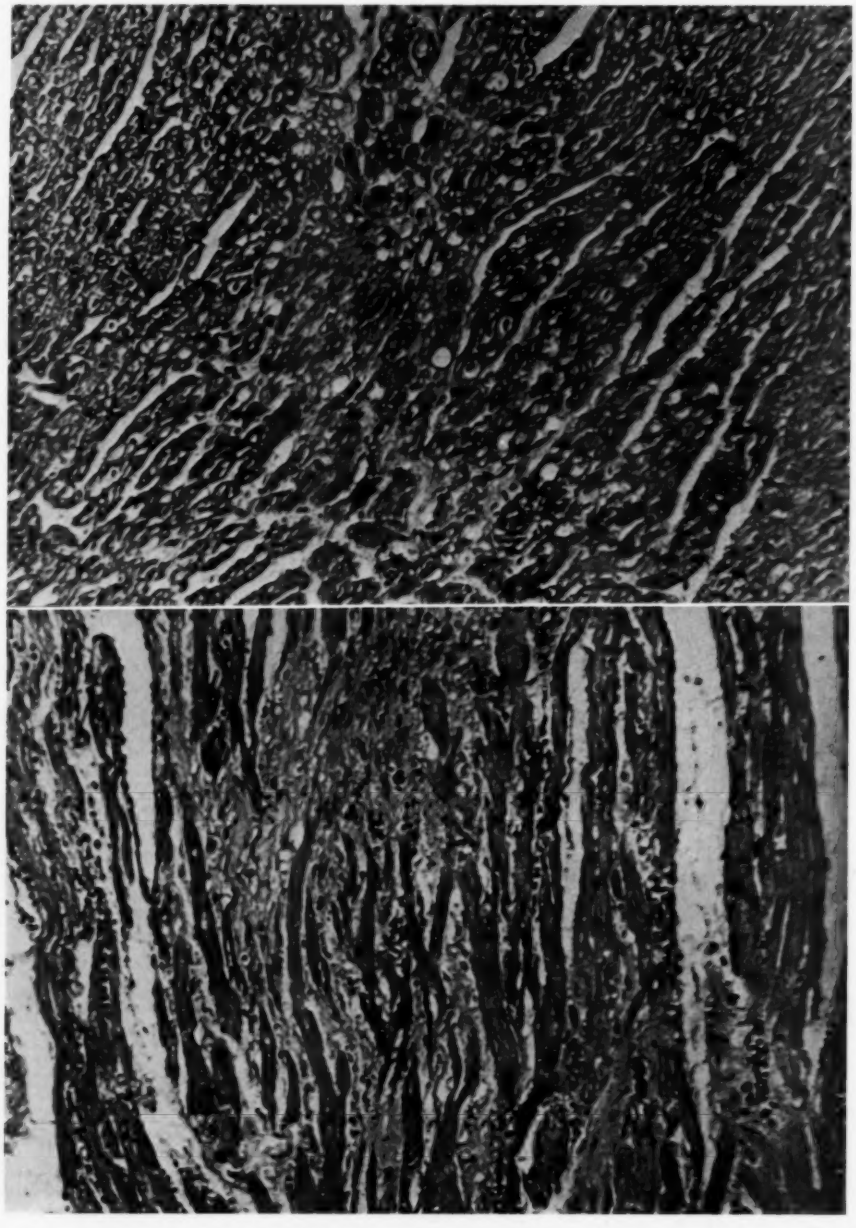


A.

B.

Fig. 3.—*A*, Marked intimal fibroelastosis, swelling and fragmentation of the lamina elastica interna, and slight irregular medial fibrosis of the arcus aortae, in rabbit No. 96, which received 8 injections of the bacterial polysaccharide (50 μg/Kg.) and adrenaline (10 μg/Kg.) within 2 weeks. (Elastica-hematoxylin-eosin stain. Magnification ×700.) *B*, Marked intimal fibrosis causing severe stenosis of the lumen at the branching part of a medium-sized coronary artery in rabbit No. 87, which received 12 injections of the bacterial polysaccharide (50 μg/Kg.) and adrenaline (10 μg/Kg.) within 5 weeks. (Elastica-hematoxylin-eosin stain. Magnification ×150.)

recognizable small scar was found in the myocardium beneath the endocardium of the left ventricle, as seen in Fig. 1. Curiously enough there was an absence of pathologic findings in the kidney, except for a slight fibrous intimal thickening of some of the arteries, even though the polysaccharide was administered repeatedly.



A.

B.

Fig. 4.—*A*, The initial stage of myocardial lesion, in rabbit No. 86, which received 12 injections of bacterial polysaccharide (50 μg/Kg.) and adrenaline (10 μg/Kg.) within 4 weeks. Eosinophilic coagulative necrosis and/or vacuolar degeneration of the muscles are very marked, and the beginning of interstitial fibrosis can be seen. (Hematoxylin-eosin stain. Magnification ×200.) *B*, The next stage of myocardial lesion, in rabbit No. 87. Early focal myocardial scars containing degenerated and atrophic muscle fibers are seen. (Hematoxylin-eosin stain. Magnification ×200.)

4. Animals receiving adrenaline, 3 or 10 μg per kilogram of body weight, following pretreatment with polysaccharide, showed severe changes of the artery and heart. As seen in Figs. 1 and 2,*A* all animals showed macroscopically visible large myocardial damage. In 1 of all 13 animals the wall of both ventricles became very thin because of myocardial degeneration, showing a giant heart aneurysm (Fig. 2,*B*). As in the third group of animals, various stages of degeneration of the myocardium (i.e., vacuolar, slight fatty degeneration, and coagulation necrosis of myofibers), myocardial fibrosis, and scars were observed. The animals which were kept alive for 12 weeks showed calcified scars. In contrast with the severe damage to their hearts, these rabbits showed no macroscopically visible changes of the aorta. Microscopically, the elastica stain of the aorta showed only the irregularity of the muscle fiber of the media and slight focal elastofibrosis of the media, but there was neither the granuloma nor necrotic foci which are common in Mönckeberg's sclerosis. The intima showed a subendothelial fibroblastic proliferation, and/or slight increase of metachromatic substance and fragmentation of the internal elastic membrane. Such a change of the intima was especially strong at or near the branching points (Fig. 3,*A*).

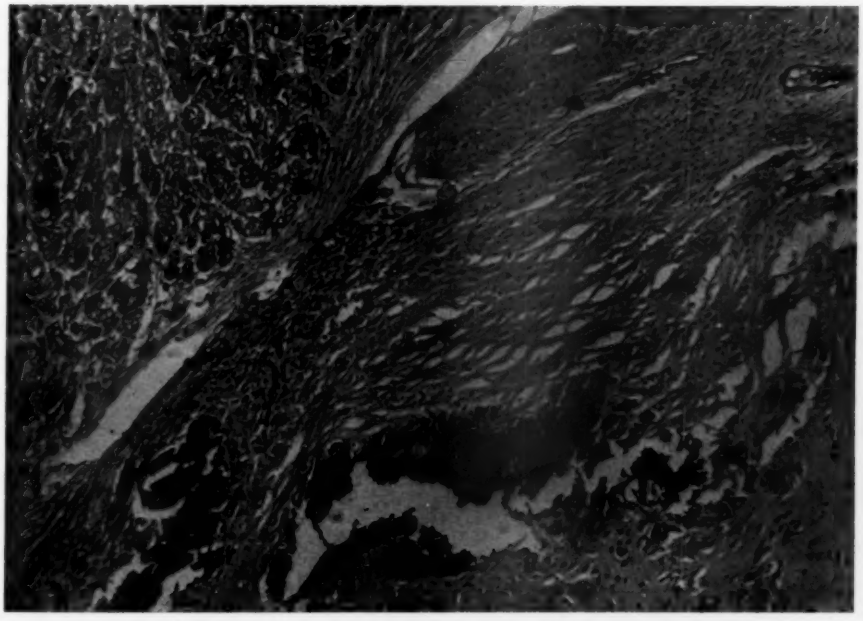


Fig. 4.—*C*, The final stage of myocardial lesion, in rabbit No. 3, which received 36 injections of the bacterial polysaccharide and adrenaline and remained alive for 12 weeks. Extensive myocardial scar with calcified necrotic muscles in the left ventricle, and interstitial fibrosis near the myocardium can also be noticed. (Hematoxylin-eosin stain. Magnification ×100.)

The other arteries showed also a characteristic change which was observed in the former experiment. The most severe change was observed in the medium-sized, small coronary arteries and arterioles which penetrate the wall of the left ventricle, and was especially great at or near the points of bifurcation (Fig. 3,*B*). On the contrary, the main coronary arteries showed a weaker change. The most

striking change of the coronary artery was the fibrous thickening of the intima similar to that of the aorta described above. Because of the thickening of the intima the lumen became narrow, but thrombosis could not be observed. The media showed a slight atrophy and histolytic edema in some cases. The adventitia was somewhat fibrous. The change in the coronary artery outside the left ventricle was also conspicuous, but was far weaker.

The artery, especially the medium-sized and small arteries of the lung, showed an elastofibrous thickening of the intima in some parts, as seen in the heart, although far weaker as compared with that in the coronary artery of the left ventricle; but in the kidney, liver, and other organs the artery showed also similar but minimal damage. The involvement of the other organs, excepting the heart and blood vessels, was not conspicuous. Here again the absence of macroscopically as well as microscopically recognizable change of kidney was noted.

Only 1 animal showed a gastric ulcer in the middle of the wall of the lesser curvature of the stomach, and died due to perforation into the peritoneal cavity.

5. Animals receiving adrenaline subsequent to pretreatment with polysaccharide, and at the same time receiving $MgCl_2$ orally, showed visible myocardial damage in only 1 of all 6 animals. The other 5 animals had no grossly visible change of the heart and arteries (Fig. 2,*C*) except a very small foci in the papillar muscle in 2 of 5 rabbits.

Microscopically, a few scattered degenerative and fibrotic foci in the myocardium beneath the endocardium of the left ventricle were observed. The medium-sized coronary artery showed a somewhat remarkable fibrous thickening of the intimal layer, but weaker as compared with that in the former group of animals without $MgCl_2$ administration. The medium-sized and small arteries and arterioles of the lung showed also a slight fibrous thickening of the intima. But the artery of the other organs, and the aorta showed almost no change, except in 2 animals in which there was a slight irregularity of the medial muscle fibers of the aorta and a very slight intimal thickening of the aorta. The organs, excepting the heart and blood vessels, were found to show no recognizable changes.

DISCUSSION

Since the investigation of Hueper,[13] some high molecular colloids have been known to induce atheroma-like lesions, and many researchers have explored the significance in atherogenesis of the state of aggregation of cholesterol in the plasma and of the physicochemical nature of the blood lipid and lipoprotein. Especially should a series of investigations by Gofman[14,15] and his collaborators be noticed.

But the appearance of myocardial lesions produced by using high molecular substances has not been reported until now.

The most important finding in this experiment is the appearance of myocardial infarct-like lesions and arterial damage, especially of the intima, by the repetitious administration of bacterial polysaccharide alone or in combination with adrenaline injection. In another experiment by the authors,[16] similar

changes were found to be produced using other high molecular substances—glycogen, dextran, and a suspensoid, kaolin. The damage to the artery and the heart seen in this experiment may not be the specific effect of the bacterial polysaccharide, but rather, a common phenomenon induced by several high molecular substances.

Similar damage to the artery and the heart were also produced in rabbits and rats by the authors employing the same procedure using several high molecular substances with or without the subsequent administration of adrenaline; this will be reported upon elsewhere.[17] This evidence may suggest that the results obtained in the present experiment in rabbits are not species-specific phenomena.

The dosage of bacterial polysaccharide used in this experiment was twice as high as that used in the former experiment,[1] and it had been confirmed in the other experiment by the authors that the administration of the polysaccharide applied in this experiment caused a precipitation of fibrinogen and clumping of platelets and leukocytes, as shown by Stetson,[7] Walton,[8] and also by Landy and Shear[6]; the effect with the dosage used in the present experiment was sufficiently strong and was far stronger in comparison with the dosage used in the former experiment.[1]

Such a difference of the effect of the polysaccharide used in this and the former experiment might be reflected in the difference of the damage to the heart in each group of animals.

It was also confirmed by the authors,[11] using an electron microscope, that the endothelial cells of the capillaries and arteries of the myocardium showed a swelling and the adherence on them of an electrodense plasma substance and platelet-leukocyte thrombi after the single administration of the polysaccharide. The repetition of such a phenomenon may be considered to result in the damage to the blood vessels and the heart as seen in this experiment.

In the additional findings with the electron microscope[11] the damage to the endothelial cells induced by the polysaccharide was found to be promoted remarkably by a subsequent administration of a smaller amount of adrenaline, as performed in this experiment.

An apparent difference in the severity of the damage to the artery and the heart between two groups of animals, one treated with bacterial polysaccharide alone and the other with bacterial polysaccharide followed by the administration of adrenaline, was noted as the second important finding in this experiment. The damage to the heart and blood vessels was stronger in the latter group of animals even though the number of injections in the latter group was smaller than in the former group.

It is well known that adrenaline and noradrenaline cause medial necrosis of the artery in rabbits, resulting in Mönckeberg's sclerosis and myocardial damage. But as was seen, the dosage of adrenaline used in this experiment was not large enough to induce medial necrosis. Nevertheless, it promoted the appearance of damage of the artery and the heart by the polysaccharide.

The lesion of the artery of the animals in this experiment seems to be due in part to intravascular stress caused by the hemodynamics of the circulation

as modified by anatomic factors, because the damage to the artery was found to be severe in the artery exposed to intravascular hemodynamic stress. The strongest damage was found regularly in the artery of the myocardium of the left ventricle and especially at or near the points of bifurcation. Needless to say, adrenaline exaggerates the hemodynamic stress and exaggerates the injuries of the endothelial cells, muscle fibers of the myocardium, and the blood vessels caused by the polysaccharide; on the other hand, it stimulates the activity of the muscle fiber of the blood vessels and the heart, resulting possibly in the appearance of excess metabolites which may cause increased adherence of the electrodense plasma substance and platelet-leukocyte thrombi on the swollen endothelial cells, as shown by the authors' electron microscopic investigation.[11]

In the authors' other experiment the administration of magnesium chloride applied in this experiment was shown to inhibit partially the effect of high molecular substance on the blood of rabbits. The evidence obtained by Vitale,[18] Hellerstein,[19] Nakamura and associates,[20] which showed the preventive effect of the magnesium compound on cholesterol atheromatosis in animals, may suggest some possible correlation of the mechanism involved in the genesis of cholesterol atheromatosis and arteriosclerosis produced by a high molecular substance in this experiment. However, the similar preventive effect of magnesium chloride as observed in the "infarctoid cardiopathy" by Selye[21] may show the complexity of the problem involved. However, the morphologic changes observed by electron microscopy,[11] as well as the changes of the blood (described in detail in the preceding paragraph) due to the single injection of polysaccharide with or without the adrenaline, as performed in this experiment, were recently shown by the authors to be inhibited effectively by the oral administration of magnesium chloride. This preventive effect of orally administered magnesium chloride on the biological effect of the high molecular substance might minimize the damage due to the repetitious administration of polysaccharide with the adrenaline.

Some of the high molecular substances are well known[6-8] to cause intravascular coagulation of the blood, precipitation of fibrinogen, and clumping of the platelets as described above. Hypercholesterolemia is also well known to enhance the coagulability of the blood. The attack by such high molecular substances on the human being may be encountered under various conditions: infections, burns, traumatic injuries, antigen-antibody reactions, and even sometimes through the ingestion of some high molecular substances.

The intradermal injection of adrenaline in human beings was shown by the authors[22] to elicit hemorrhagic necrosis under various conditions, i.e., infections of various bacteria (including *Shigella paradysenteriae*, *Shigella sonnei*, *Salmonella typhi*, *Salmonella paratyphi*, *Escherichia coli*, and *Bacillus diphtheriae*), ileus, colitis, some cases of obstipation, allergic conditions, injuries including operation, burns, blood transfusion, some cases of hypertension, nephritis, and myocardial infarction similar to that in the animals which were under the effect of high molecular substances used in this experiment. Also, the ingestion of such high molecular substance was found by the authors[22] to cause the same conditions in animals and human beings.

Under the stress of modern life the invasion of such high molecular substances, whether of exogenous or endogenous origin, which cause damage to the blood vessels and the myocardium, may be considered to have a significance in the etiology of not only human arteriosclerosis but also of myocardial infarction, especially among people whose blood shows increased tendency to coagulate because of hypercholesterolemia and to infiltrate the cholesterol into the damaged intima. Here further investigation is needed.

SUMMARY

In rabbits the repetitious administration of a small amount of a high molecular substance, i.e., bacterial polysaccharide prepared from a strain of *Shigella flexneri 2b*, which is capable of eliciting intravascular blood coagulation, precipitating fibrinogen, clumping the platelets and leukocytes, inducing swelling of endothelial cells and the adherence on them of electrodense plasma substance and platelet-leukocyte thrombi, induced a subendothelial fibroblastic proliferation, deposition of a metachromatic substance, and fragmentation of the internal elastic membrane in the coronary artery and in some of the other arteries (e.g., of the lung), and grossly visible infarct-like lesions in the myocardium of the left ventricle and also microscopically recognizable scar and fibrotic and degenerative foci in the myocardium beneath the endocardium of the left ventricle.

Repetitious administration of the bacterial polysaccharide in combination with subsequent administration of a small amount of adrenaline, which by itself induces no recognizable change of the blood vessels and the heart, except for a few and microscopically small degenerative foci in a limited area of the myocardium, induced visibly large infarct-like lesions in the myocardium of the left ventricle and strong damage to the artery, especially of the medium-sized and small arteries and arterioles located inside the myocardium of the left ventricle, as in the case of animals treated with polysaccharide, but far stronger. The aorta showed also a similar change in the intimal layer and slight irregularity in the medial myofibers. Otherwise, no sclerosis of the Mönckeberg type was found. The other organs, including the kidney, showed no recognizable change, except in one animal which showed gastric ulcer perforating into the abdominal cavity.

The damage to the heart and the blood vessels, caused by the bacterial polysaccharide, was considered as a common phenomenon induced by some of the high molecular substances, and not as a species-specific phenomenon. Such damage was reduced effectively by the concurrent oral administration of magnesium chloride.

This article is dedicated to Prof. Horace W. Magoun of the University of California at Los Angeles. The work was done with the kind collaboration of Prof. Miyamoto, Dr. Kariyone, Prof. Okada, Prof. Akiba, Prof. Ohta, Dr. Ohtsu, and Dr. Sano.

REFERENCES

1a. Shimamoto, T., Fujita, T., Shimura, H., Konishi, T., Iwahara, S., and Yajima, G.: Proc. Japan. Acad. **33**:692, 1957.

1b. Shimamoto, T., Fujita, T., Shimura, H., Konishi, T., Sano, T., and Yajima, G.: Clin. of Japan. **4**:145, 1958.
2. Shimamoto, T., Yamazaki, H., Ohno, K., Uchida, H., Konishi, T., and Iwahara, S.: Proc. Japan. Acad. **34**:444, 1958.
3. Shimamoto, T., Yamazaki, H., Sagawa, N., Iwahara, S., Konishi, T., and Maezawa, H.: Proc. Japan. Acad. **34**:450, 1958.
4. Shimamoto, T., Tajimi, H., and Iwahara, S.: Japan. Med. J. **1785**:3, 1958.
5. Shimamoto, T., and Konishi, T.: Japan. Clin. **16**:1087, 1958.
6. Landy, M., and Shear, M.: J. Exper. Med. **106**:77, 1957.
7. Stetson, C. A.: J. Exper. Med. **93**:489, 1951.
8. Walton, K. W.: Brit. J. Pharmacol. **9**:1, 1954.
9. Thomas, L.: J. Exper. Med. **104**:865, 1956.
10a. Shimamoto, T.: Proc. Japan Acad. **33**:498, 1957.
10b. Shimamoto, T., Konishi, T., Yamazaki, H., Inoue, M., and Fujita, T.: Jap. Med. J. **1717**:5, 1957.
11. Shimamoto, T., Fujita, T., Shimura, H., Yamazaki, H., Iwahara, S., and Yajima, G.: (Data to be published.)
12. Pappas, G. D., Ross, M. H., and Thomas, L.: J. Exper. Med. **107**:333, 1958.
13. Hueper, W. C.: Arch. Path. **31**:11, 1941.
14. Gofman, J. W., Lindgren, F. T., and Elliott, H.: J. Biol. Chem. **179**:973, 1949.
15. Jones, H. B., Gofman, J. W., Lindgren, F. T., Lyon, T. P., Graham, D. M., Strisower, B., and Nichols, A. V.: Am. J. Med. **11**:358, 1951.
16. Shimamoto, T., Fujita, T., Shimura, H., Yamazaki, H., Iwahara, S., and Yajima, G.: Proc. Japan Acad. (In press.)
17. Shimamoto, T., Fujita, T., Shimura, H., Yamazaki, H., Tazaki, M., Iwahara, S., and Yajima, G.: (Data to be published.)
18. Vitale, J. J., White, P. D., Nakamura, M., Hegsted, D. M., Zamchek, N., and Hellerstein, E. E.: J. Exper. Med. **106**:757, 1957.
19. Hellerstein, E. E., Vitale, J. J., and Zamchek, N.: Fed. Proc. **16**:359, 1957.
20. Nakamura, M., Vitale, J. J., Hellerstein, E. E., and Hegsted, D. M.: Fed. Proc. **17**:486, 1958.
21. Selye, H.: Am. Heart J. **55**:805, 1958.
22. Shimamoto, T.: Medicine **14**:795, 1957.

Hypoplasia of the Aorta: Report of a Case

Kalevi Pyörälä, M.D., Per-Erik Heikel, M.D., and Pentti I. Halonen, M.D.
Helsinki, Finland

Hypoplasia of the aorta has been defined by Abbot[1] as a condition in which the arterial vessels in the greater circulation remain abnormally small. This anomaly, first described by Morgagni,[23] in 1761, was well known to the clinicians of the nineteenth century. Until 1907, when von Ritook[26] dealt with this subject, some 100 cases had been reported. Surprisingly little attention has since been paid to aortic hypoplasia. Thereafter, only 20 cases have been reported in which hypoplasia of the whole aorta has been considered to be the cause of a fatal cardiac failure.[4,5,7,10,13,15,16,21,22,24,28,30-32] The name "aortic hypoplasia" is sometimes used for cases in which only part of the aorta is hypoplastic. Cases of this kind are not dealt with in this paper.

The congenital etiology of aortic hypoplasia was first suggested by Meckel,[20] in 1768. Rokitansky[27] and Wirchow[33] also considered aortic hypoplasia to be a congenital anomaly. According to Burke[9] and von Ritook,[26] postnatal retardation in the growth of the aorta is an important factor in the development of aortic hypoplasia.

Normal measurements of the aorta vary according to age, sex, and constitution. The diagnosis of aortic hypoplasia must be based upon knowledge of normal lower limits. The most extensive work on normal aortic measurements at autopsy is probably that made by Kaufman[17] during World War I. The frequency of aortic hypoplasia varies greatly in autopsy materials, which fact may be due to the differing criteria used. Aortic hypoplasia may also be overlooked sometimes, if special attention is not paid to it. Ikeda[16] studied autopsy records of Minnesota University up to 1930, and found 8 cases of aortic hypoplasia in 14,305 autopsied cases. Peculiarly, all of these 8 cases were diagnosed before 1917. Five of these patients had a hypoplastic heart, 2 showed a slight hypertrophy of the ventricles, and 1 had a ventricular septal defect. None of them had died of heart failure. Werley, Waite, and Kelsey[31] have also pointed out that a hypoplastic aorta, without any signs of heart failure, is sometimes observed at autopsy. These writers found 25 recorded cases of aortic hypoplasia in the 4,500 autopsies performed by the Department of Pathology of the University of Texas.

From the Hospital of the Wihuri Research Institute, Helsinki, Finland.
Received for publication Oct. 6, 1958.

Five of these 25 cases had associated anomalies. Only 4 of them showed cardiac enlargement. Apparently, hypoplasia of the aorta as a coexisting anomaly in congenital cardiovascular diseases is not rare. In 1,000 autopsied cases of congenital heart disease reported in the literature, Abbot[3] found 75 cases in which aortic hypoplasia was associated with other cardiovascular anomalies, but only 2 cases of isolated hypoplasia of the aorta. Aortic hypoplasia is not uncommon in cases of coarctation of the aorta. In a study of 200 recorded cases of coarctation of the aorta, Abbot[2] found 21 cases in which aortic hypoplasia was mentioned as an associated finding.

Most of the cases of isolated aortic hypoplasia reported in the literature have occurred in males. In the cases in which a fatal cardiac failure has been attributed to aortic hypoplasia, the symptoms of cardiac failure have appeared rather rapidly at the age of 15 to 30 years. In some cases, death has occurred suddenly, without any preceding symptoms of cardiac failure.

Hypertrophy of the left ventricle, often remarkable and associated with dilatation, has been the most frequent autopsy finding in cases of aortic hypoplasia. Right ventricular hypertrophy, with or without dilatation, has also frequently been observed in these cases. In some cases, however, a hypoplastic heart has been observed. In the 2 cases reported by Habay[15] and de Mey[22] the left ventricle was hypoplastic, whereas the right ventricle showed a marked hypertrophy.

The clinical diagnosis of aortic hypoplasia has been made in only a few cases. Before x-ray examination came into use, the diagnosis of aortic hypoplasia, later verified at autopsy, was made in some cases on the basis of clinical findings.[6,12] Stoerk,[29] in 1912, called attention to the small size of the aortic shadow at x-ray examination in cases of aortic hypoplasia. This finding led to a correct clinical diagnosis in one of the cases reported by Werley, Waite and Kelsey.[31]

Modern cardiological methods, especially angiocardiography and aortography, are the most exact means for the clinical diagnosis of aortic anomalies. However, despite the present widespread use of these methods in the study of cardiovascular diseases, only little attention has been paid to hypoplasia of the aorta. Bulgarelli[8] reported a case in which hypoplasia of the aorta was demonstrated by angiocardiography. Additional findings in this case were an infundibular aortic stenosis and hypoplasia of the pulmonary artery. Catheterization showed a pressure of 160/10 mm. Hg in the right ventricle. Basso and di Paolo[7] reported a case in which an isolated aortic hypoplasia, later verified at autopsy, was diagnosed by angiocardiography. The purpose of this paper is to report a case of aortic hypoplasia studied by catheterization of the right heart and by angiocardiography. This case is especially interesting, because it showed some clinical features simulating aortic coarctation.

CASE REPORT

A 6-year-old boy was first admitted to the Hospital of the Wihuri Research Institute on Nov. 16, 1949.

The mother of the boy had been well during the pregnancy. The younger sister and brother of the patient were healthy. The birth weight of the patient was 2,500 grams. After birth the

child was weak and could not suckle. Teeth appeared at the usual age. He began to talk in his second year and learned to walk at the age of 2 years. The mental development of the child was clearly retarded. On physical exertion he tired more readily than other children of the same age. A heart murmur was detected when the child was 4 months old. The murmur had been so loud that it was sometimes heard at a distance.

Physical examination on admission revealed a thinly built boy, who had no cyanosis or clubbing. The heaving apex beat was felt in the normal place. Both carotid arteries showed a visible pulsation, which was also observed at both infraclavicular areas. A gross systolic thrill was felt at the right sternal border in the second intercostal space, at both infraclavicular areas, and along both carotid arteries. A Grade 5 systolic ejection murmur was best heard above the sternum at the level of the second intercostal space. The murmur was transmitted over the entire precordium, to the neck, and also to the back. A short systolic bruit was heard on both brachial arteries, along the abdominal aorta, and on both femoral arteries. Peripheral arterial pulsations were somewhat weaker in the right upper limb than in the left. Pulsations of both femoral arteries, as well as the more peripheral pulsations in both lower limbs, could be felt well. The blood pressure (mm. Hg) was 160/60 in the right arm, 200/50 in the left arm, 140/60 in the right leg, and 130/60 in the left leg. No pulsations could be felt in the intercostal spaces. No pulmonary râles were heard, and the liver was not enlarged. The hemoglobin was 12.8 Gm. per 100 ml., and the hematocrit was 44 per cent.

X-ray examination of the chest showed no abnormalities of the ribs. The heart was of normal size and shape (total volume, 180 c.c. = 320 c.c./sq. M. of body surface). No aortic knob could be seen. The pulmonary arterial segment, hilar shadows, and peripheral vascularity of the lungs were normal.

The electrocardiogram (Leads I, II, III, and CR_4) showed a sinus rhythm with a frequency of 95 per minute. The duration of P wave was 0.08 sec., P-R time was 0.11 sec., the duration of the QRS complex was 0.07 sec., and the Q-T time was 0.29 sec. $\hat{A}P$ was $+75°$, $\hat{A}QRS$ was $+100°$, $\hat{A}T$ was $-50°$. The P wave was notched in Leads I and CR_4. The S-T segment was depressed and the T wave negative in Leads II and III.

A presumptive diagnosis of aortic coarctation was made on the basis of blood pressure findings. The parents were advised to bring the child for a new examination some years later.

The boy was seen for the second time on April 1, 1955, at the age of 12 years. He still had slight dyspnea on exertion. At the age of 9 he had learned to write and read a little.

The findings on physical examination were essentially the same as those on the first admission. The blood pressure (mm. Hg) was 200/90 in the right arm, 220/90 in the left arm, 150/90 in the right leg, and 140/90 in the left leg. X-ray and electrocardiographic findings had remained unchanged.

The patient was admitted to the hospital for a new examination on Aug. 8, 1957. The dyspnea on exertion had become somewhat worse during the last 2 years.

Findings on physical examination were the same as before. The boy's height was 156 centimeters, and his weight was 43 kilograms. The blood pressure (mm. Hg) was 190/80 in the right arm, 205/80 in the left arm, 160/90 in the right leg, and 150/90 in the left leg. According to the psychiatrist's opinion, the intelligence of the boy corresponded to that of a 6-year-old child.

Ophthalmoscopic examination revealed extremely narrow, but otherwise normal retinal arteries which showed no pulsations. The fundi showed no other abnormalities.

The hemoglobin was 12.1 Gm. per 100 ml., and the hematocrit was 42 per cent. The serum cholesterol was 208 mg., and the nonprotein nitrogen was 20 mg. per 100 ml. The urine gave negative test for albumin, and the urinary sediment showed nothing abnormal. Concentration and dilution tests gave normal results. Urinary excretion of catechol amines was 50 μg during 24 hours. The I^{131} uptake of the thyroid was normal.

X-ray examination of the chest (Fig. 1) showed no notching of the ribs. The heart was of normal size and shape (430 c.c. = 380 c.c./sq. M. of body surface). The aortic knob could not even now be seen with certainty. The thoracic aorta seemed to be very narrow even in all oblique views.

Urography revealed no abnormalities in the kidneys or ureters. The skeletal age of the patient corresponded to his physiologic age.

The electrocardiogram (Fig. 2) showed a sinus rhythm with a frequency of 95 per minute. The duration of the P wave was 0.10 sec., P-R time was 0.14 sec., the duration of the QRS complex was 0.07 sec., and the Q-T time was 0.30 sec. The position of the heart was vertical, with clockwise rotation. ÂP was +45°, ÂQRS was +105°, and ÂT was −75°. The P wave was notched in Leads I, aV_L, and V_2-V_6. A qRr's type of complex and a negative T wave were observed in Lead V_1. R/S was 12/48 in Lead V_3, 23/40 in Lead V_4, 30/13 in Lead V_5, and 26/2 in Lead V_6. Intrinsicoid deflection time was 0.04 sec. in Leads V_5 and V_6. The T wave was negative in Lead V_6. The electrocardiographic findings were interpreted as suggesting left ventricular hypertrophy.

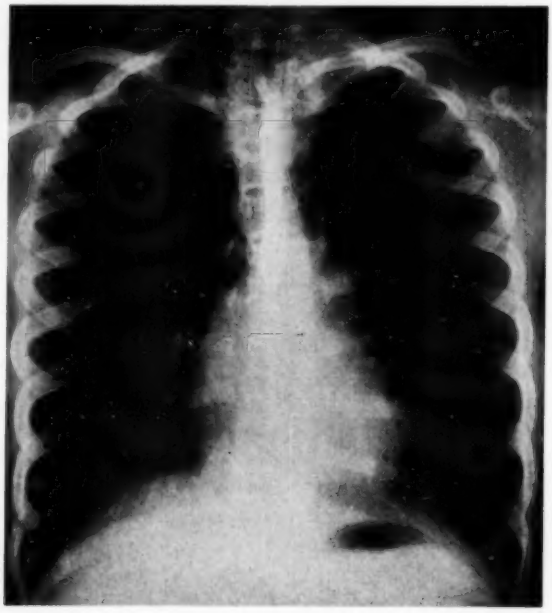


Fig. 1.—Posteroanterior chest film showing a heart of normal size. The aortic knob is absent.

Phonocardiograms showed an ejection-type systolic murmur over the entire precordium (Fig. 3). The second sound at the pulmonary area was closed in expiration and showed a splitting of 0.04 sec. in inspiration. The amplitude of the pulmonary component of the second sound was about half that of the aortic component. Indirect carotid tracing showed an anacrotic notching and a slight delay of the upstroke of the pulse wave (Fig. 3). The incisura was not clearly defined. The time from the onset of the pulse wave to the beginning of the sharp downstroke was 0.20 sec. The onset and peak of the pulse wave in the simultaneously recorded indirect femoral tracing occurred 0.05 sec. later than the corresponding events in the carotid pulse.

Velocity ballistocardiogram recorded with an electromagnetic apparatus of the Dock type showed normal H-I-J-K complexes with great respiratory variations.

Right heart catheterization was performed under a slight barbiturate premedication. The oxygen content of the blood in the venae cavae, right atrium, right ventricle, and pulmonary artery varied from 13.5 to 13.8 volumes per cent (O_2 saturation, 73 to 75 per cent). Oxygen saturation in the femoral artery was 97.5 per cent (oxygen content, 17.6 volumes per cent). The mean pulmonary artery wedge pressure was 7 mm. Hg, pulmonary arterial pressure was 30/5 mm. Hg, right ventricular pressure was 30/0 mm. Hg, right atrial pressure was 3/0 mm. Hg, and the pressure in the right femoral artery was 120/70 mm. Hg. Oxygen consumption was 206 c.c. per minute. Cardiac output, determined according to the Fick principle, was 5.43 L./min. = 4.81 L./min./M.^{2} of body surface. Cardiac output was also determined by the dye-dilution method. The dye (T-1824) was injected into the right antecubital vein, and the collection of blood samples was

made from the right femoral artery. Cardiac output determined by this method was 5.86 L./min. = 5.19 L./min./M.^{2} of body surface. The blood volume was 4.40 L. = 3.89 L./M.^{2} of body surface. The dye-dilution curve showed an appearance time of 4 sec., a peak concentration time of 9 sec., and a systemic recirculation time of 17 sec. The shape of the dye-dilution curve was normal.

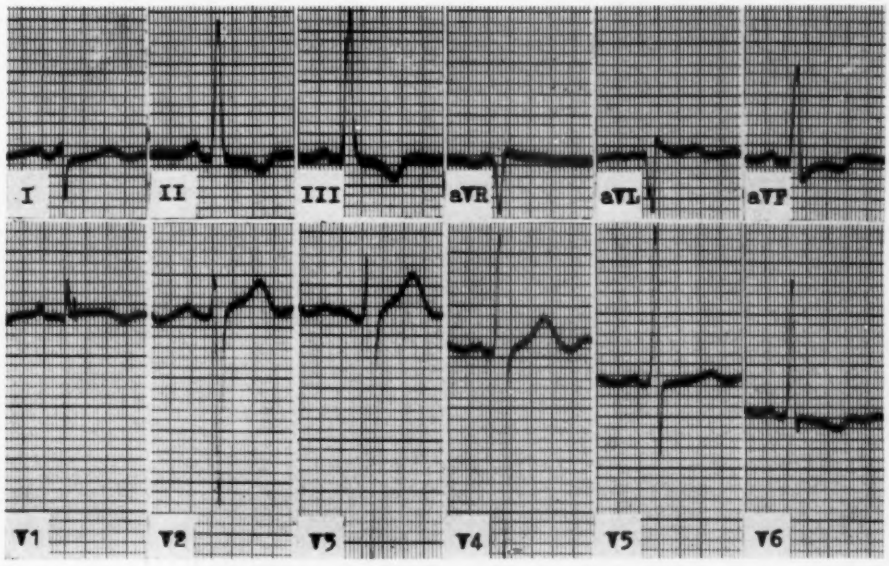


Fig. 2.—Electrocardiogram showing left ventricular hypertrophy.

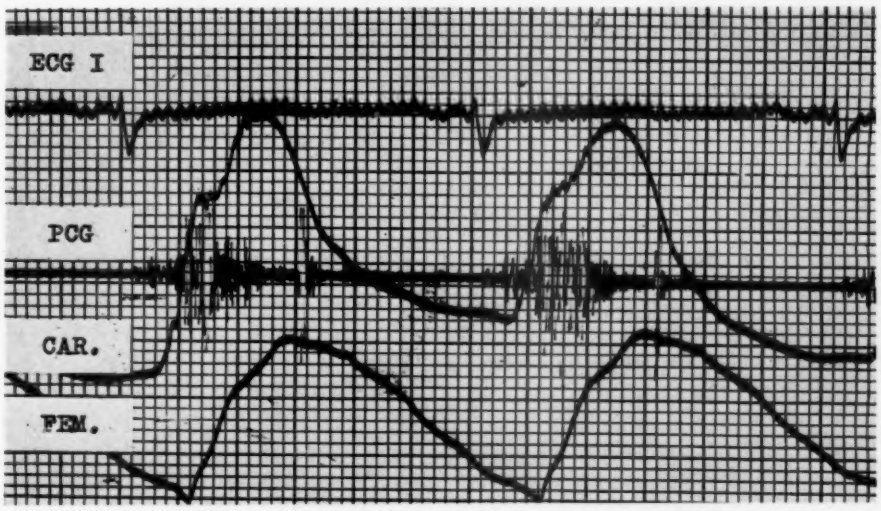
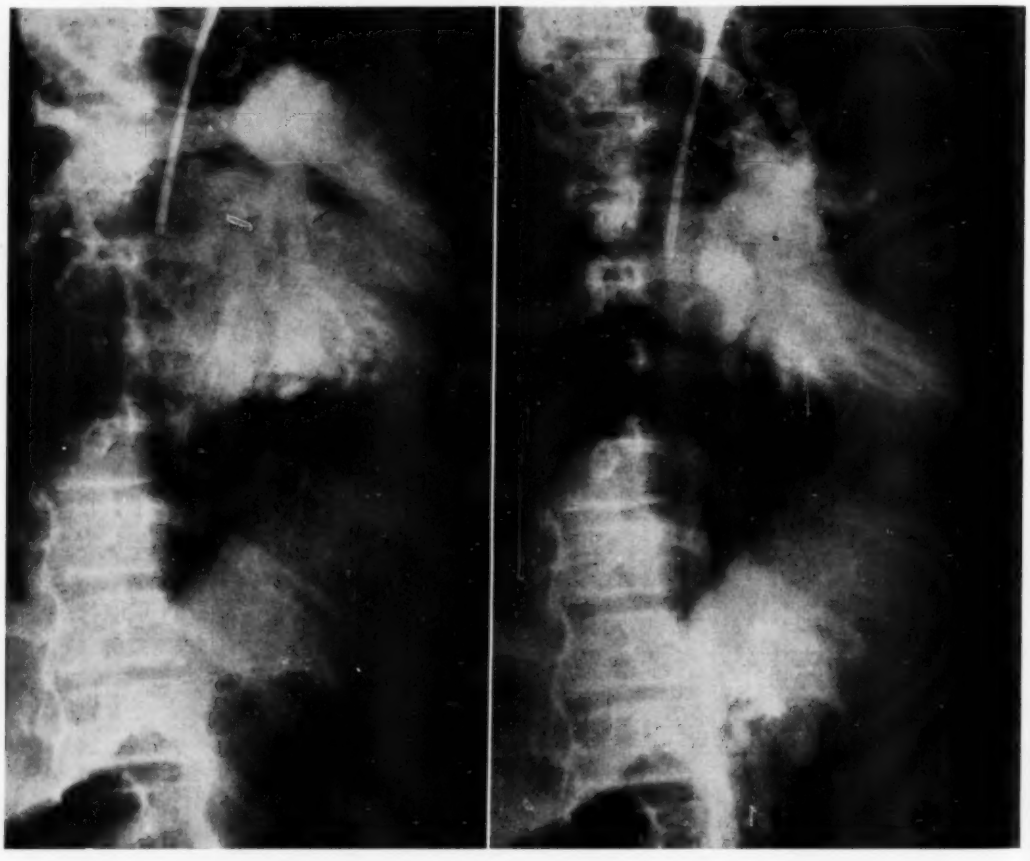


Fig. 3.—Logarithmic phonocardiogram from the aortic area, with indirect carotid and femoral tracings. Ejection-type systolic murmur with anacrotic notching and slight delay of the upstroke of the carotid pulse. The femoral pulse is not abnormally delayed as compared with the carotid pulse.

Because hypoplasia of the aorta was suspected on the basis of the absence of the aortic knob in x-ray pictures, angiocardiography was performed by placing the catheter tip in the superior vena cava. Angiocardiograms showed a right atrium and right ventricle of normal size and shape. The ventricular septum bulged remarkably to the right. The main pulmonary artery and its branches were of normal size (Fig. 4,*A*). The pulmonary veins showed nothing abnormal and

drained to the left atrium, which was of normal size. The left ventricle was somewhat dilated and its wall seemed to be hypertrophic. The size of the left ventricular infundibulum was normal. The apparently normal aortic valve was located somewhat higher than usual. The aorta was extremely narrow immediately beyond the valve. The whole aorta was uniformly hypoplastic so far as it could be followed in the angiocardiograms (Fig. 4,*B*). The diameter of the aorta measured from the films was 9 mm. just above the aortic valve. This corresponds to a corrected value of 8 mm. when the magnifying factors are taken into account. The corrected diameter was 8 mm. in the middle of the descending aorta, and 8 mm. at the level of the first lumbar vertebra. The corrected diameter of the main pulmonary artery just above the pulmonary valve was 24 mm.



A. *B.*

Fig. 4.—Right anterior oblique angiocardiograms. *A*, A film taken during systole, 2.0 sec. after the beginning of the injection. Right atrium, right ventricle, and pulmonary arterial tree are filled with contrast. The pulmonary artery and its branches are of normal size. *B*, A film taken during systole, 5.2 sec. after the beginning of the injection. Left atrium, left ventricle, and aorta are filled with contrast. The aorta is seen to be extremely hypoplastic.

DISCUSSION

In the case reported, hypoplasia of the aorta was suspected because the aortic shadow could not be seen at x-ray examination. Angiocardiograms revealed a remarkable aortic hypoplasia. The diameter of the aorta was considerably below the normal values observed in the angiocardiographic studies of Dotter

and Steinberg.[11] The systolic ejection murmur and abnormalities in the upstroke of the carotid pulse may be caused by the stenosis formed by the hypoplastic aorta to the left ventricular outflow. The finding of extremely narrow retinal arteries on ophthalmoscopy is an interesting clinical feature. As early as 1894, von Grósz[14] pointed out the significance of this sign in the diagnosis of the hypoplasia of the arterial system.

The blood pressure has been mentioned in 15 cases of aortic hypoplasia.[4-8,10,16,22,30,31] Low normal values or distinctly low pressures were observed, except in 2 cases[10,31] in which an increased pulse pressure was found. Most of the patients had a congestive heart failure at the time of examination. In our case the systolic pressure was considerably increased, whereas the diastolic pressure was normal. Determination of cardiac output and blood volume gave values somewhat higher than normal values in our laboratory. Hyperkinetic circulation in a hypoplastic arterial system might explain the increased pulse pressure in our case. Experimental[18] and clinical[25] observations have shown that the systolic pressure in the peripheral arteries of the limbs is often distinctly higher than that in the aorta. Therefore, no certain conclusions on the central arterial pressure can be drawn on the basis of indirect measurements of the arterial pressure in the peripheral arteries of the limbs. It may be assumed, however, that the left ventricular pressure must be elevated in order to expel the blood through the hypoplastic aorta when a cardiac output of normal magnitude is to be maintained.

In the case reported the systolic pressure in the lower limbs was lower than that in the upper limbs. This finding first led us to a diagnosis of aortic coarctation. The blood pressure in the lower limbs is mentioned in 2 cases of aortic hypoplasia. In the case described by Valentine and Nicholl[30] the blood pressure was 130/80 mm. Hg in the upper limbs and 110/70 mm. Hg in the left leg, and could not be measured in the right leg. At autopsy the hypoplastic aorta showed progressive narrowing beyond the origin of the thoracic and abdominal branches, and the right common iliac artery showed an anomalous origin from the right spermatic artery. In the case reported by Basso and di Paolo[7] the blood pressure was 125-130/70 mm. Hg in the upper limbs and 140-145/70 mm. Hg in the lower limbs. In our case the exact anatomy of the lower abdominal aorta and iliac arteries is not known, because these were not seen in angiocardiograms. Aortography was not considered justified, because it was clear that surgical treatment of this case would have been impossible.

Electrocardiographic findings in our case suggested hypertrophy of the left ventricle. Electrocardiographic findings including unipolar precordial leads have been mentioned in 5 cases of aortic hypoplasia. In the case reported by Delcourt, Denolin and Lequime[10] the electrocardiogram showed a partial atrioventricular block and a complete left bundle branch block, and in the case described by Alvino[4] atrial fibrillation and a complete left bundle branch block were observed. In the case reported by Basso and di Paolo[7] the electrocardiogram suggested left ventricular hypertrophy. The 2 cases described by Habay[15] and de Mey,[22] in which hypoplasia of the aorta was associated with hypoplasia of

the left ventricle and remarkable hypertrophy of the right ventricle, showed electrocardiographic signs of right ventricular hypertrophy. These 2 cases may be closely related to the syndrome "grosse pulmonaire-petite aorte" of the French writers.[19] In the case described by Bulgarelli[8] aortic hypoplasia was associated with infundibular aortic stenosis and hypoplasia of the pulmonary artery, and catheterization showed a greatly increased right ventricular pressure. In this case the electrocardiogram showed a combined ventricular hypertrophy.

Autopsy findings in cases of aortic hypoplasia suggest that hypoplasia of the aorta of extreme degree causes a strain on the left ventricle, resulting in left ventricular hypertrophy and failure, which is apparently followed by passive pulmonary hypertension and right ventricular hypertrophy. Hemodynamic disturbances caused by aortic hypoplasia have not been studied by modern cardiological methods. In our case, catheterization of the right heart revealed normal hemodynamics in the pulmonary circulation. Angiocardiography showed a normal right ventricle and pulmonary artery and a somewhat dilated and apparently hypertrophic left ventricle. The physical disability of the patient was still rather slight.

Aortic hypoplasia should be considered as an etiological factor of obscure cardiac hypertrophy and failure in young individuals. It should also be included in the differential diagnosis in cases of congenital heart disease. Cases of aortic hypoplasia may sometimes show features simulating coarctation of the aorta.

SUMMARY

A case of solitary hypoplasia of the aorta in a 14-year-old boy is reported. The suspicion of aortic hypoplasia was aroused by the absence of the aortic knob at x-ray examination. Angiocardiography showed an extreme hypoplasia of the aorta. Catheterization of the right heart revealed normal hemodynamics in the pulmonary circulation.

The systolic blood pressure in the arms was remarkably elevated, but the diastolic pressure was normal. The systolic pressure in the legs was lower than that in the arms. This finding first led to the diagnosis of coarctation of the aorta. An interesting clinical feature was the finding of extremely narrow retinal arteries on ophthalmoscopy.

Aortic hypoplasia should be considered in the differential diagnosis in cases of obscure cardiac failure in young individuals and in cases of congenital heart disease.

REFERENCES

1. Abbot, M.E.: *in* Osler, W., and McCrae, T.: Modern Medicine, Vol. 4, Philadelphia, 1927, Lea & Febiger.
2. Abbot, M. E.: AM. HEART J. **3**:381, 1928.
3. Abbot, M. E.: *in* Nelson's New Loose Leaf Medicine, Ed. 18, Vol. 4, New York, 1937, Nelson & Sons.
4. Alvino, A.: Minerva med. (parte sc.) **44**:350, 1953.
5. Andersen, J., and Nyfos, L.: Acta med. scandinav. **146**:325, 1953.
6. Apelt, F.: Deutsche med. Wchnschr. **31**:1186 and 1233, 1905.

7. Basso, U., and di Paolo, E.: Arch. ital. anat. istol. patol. **30**:446, 1956.
8. Bulgarelli, R.: Minerva pediat. **8**:1373, 1956.
9. Burke, J.: Deutsches Arch. klin. Med. **71**:189, 1901.
10. Delcourt, R., Denolin, H., and Lequime, J.: Acta cardiol. **3**:144, 1948.
11. Dotter, C. T., and Steinberg, I.: Radiology **52**:353, 1949.
12. Fraenzel, O.: Deutsche med. Wchnschr. **14**:589, 1888.
13. Frühwald, V.: Deutsche med. Wchnschr. **39**:889, 1913.
14. von Grósz, E.: Quoted by von Ritook.[26]
15. Habay, G.: Bruxelles-méd. **30**:1051, 1950.
16. Ikeda, K.: Minnesota Med. **16**:172, 1933.
17. Kaufman, L.: *in* Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, 1924, J. Springer.
18. Laszt, L., and Müller, A.: Helvet. physiol. et pharmacol. acta **10**:469, 1952.
19. Laubry, C., Routier, D., and Heim de Balzac, R.: Bull. et mém. Soc. méd. hôp. Paris **56**:810, 1940.
20. Meckel, J. F.: Quoted by Burke.[9]
21. Melchior, E.: Deutsche med. Wchnschr. **39**:160, 1913.
22. de Mey, D.: Acta cardiol. **9**:77, 1954.
23. Morgagni, G. B.: Quoted by Burke.[9]
24. Philpott, N. W.: Ann. Int. Med. **2**:948, 1929.
25. von Recklinghausen, H.: Blutdruckmessung und Kreislauf in den Arterien des Menschen, Kreislauf-Bücherei, Bd. IV, Leipzig, 1940, Steinkopff.
26. von Ritook, S.: Ztschr. klin. Med. **61**:32, 1907.
27. Rokitansky, C.: Quoted by Burke.[9]
28. Sarri, U.: Policlinico (sez. prat.) **26**:9, 1919.
29. Stoerk, E.: Medizinische Klinik **8**:1227, 1912.
30. Valentine, W. N., and Nicholl, R. J.: Am. Heart J. **30**:514, 1945.
31. Werley, G., Waite, W. W., and Kelsey, M. P.: Texas J. Med. **39**:467, 1944.
32. Whittle, C. H.: Lancet **216**:1354, 1929.
33. Wirchow, R.: Quoted by Burke.[9]

Isolated Congenital Pulmonic Valvular Regurgitation

B. L. Lendrum, M.D., and A. B. Shaffer, M.D., Chicago, Ill.

Congenital pulmonic valvular regurgitation, unassociated with other cardiovascular lesions, is rare. Only nine cases, in which the diagnosis was made antemortem by means of cardiac catheterization or at surgery, are recorded in medical literature.[1-6,8] The long-term prognosis of this lesion is unknown, and since most patients observed have been asymptomatic, the apparently benign nature of the lesion has been stressed. Certain clinical, anatomic, and hemodynamic studies, involving experimentally produced pulmonic regurgitation in dogs, likewise emphasize the apparent absence of symptoms and physiologic handicap due to the lesion.[9,10] Reports of two patients with apparently uncomplicated isolated pulmonic valvular regurgitation who did have symptoms,[3,8] together with several recent experimental studies indicating that right ventricular dilatation and even congestive failure can follow production of severe pulmonic valvular regurgitation,[11-13] suggest that the lesion is not always benign.

Because of its rarity, and because certain hemodynamic aspects of the lesion have been inadequately considered in the past, the following report of a case of isolated congenital pulmonic valvular regurgitation is submitted.

CASE REPORT

R. A., a 16-year-old white boy, previously in good health, was admitted in March, 1958, with a diagnosis of moderately severe diabetic acidosis of sudden onset. He was known to have had a heart murmur in infancy. The presence of this murmur and an electrocardiogram interpreted as abnormal led to his referral for cardiac work-up following control of the diabetes. There was no history suggestive of acute rheumatic fever, nor was there a striking incidence of infection of the upper respiratory tract. Growth and activity were normal, and he participated in vigorous competitive sports. Review of cardiovascular symptoms was negative.

The patient appeared to be of stated age, was 6 feet tall, and weighed 115 pounds. The pulse rate was 64 per minute, and the respiratory rate was 18 per minute. The blood pressure was 120/70 mm. Hg in both arms, and 120/60 mm. Hg in both legs. The remainder of the examination was negative except for cardiac findings. There was a faint systolic thrill in the second left intercostal space near the sternum. A Grade 2 to 3, harsh systolic murmur was best heard in this location and radiated down the left sternal border. A somewhat more intense, harsh, early diastolic decrescendo murmur was also heard maximally in the second left intercostal space parasternally.

From the Cardiovascular Department, Medical Research Institute and the Pediatrics Department, Michael Reese Hospital, Chicago, Ill.

Aided by grants from the National Heart Institute and the Kunstadter Fund.

Received for publication Sept. 25, 1958.

The second heart sound in the pulmonary area was of normal intensity, and was distinctly, possibly abnormally, split. There were no other positive findings referable to the cardiovascular system.

X-ray examination (Fig. 1) revealed a heart of normal size, with no specific chamber abnormality in any projection. The aortic knob was small. The lung fields were of normal vascularity. The main and left pulmonary arteries were prominent. On fluoroscopy, these vessels pulsated vigorously and there was a suggestion of hilar dance. The electrocardiogram was suggestive of incomplete block of the right bundle branch system (Fig. 2). A diagnosis of isolated pulmonic valvular regurgitation, presumably congenital, was made.

The results of right heart catheterization are shown in Table I. There was no demonstrable shunting of blood in either direction. The right ventricular systolic and end-diastolic pressures were at the upper limits of normal (Fig. 3). The systolic pressure of the main pulmonary artery was about 12 mm. Hg below that of the right ventricle, while the end-diastolic pressure of the pulmonary artery closely approximated that of the right ventricle. This close approximation of end-diastolic pressures in the right ventricle and in the pulmonary artery is characteristic of pulmonic valvular regurgitation.[13] The pressure curve recorded from the pulmonary artery near the pulmonic valve (Fig. 4) showed the steep dicrotic slope which is also referred to as characteristic of pulmonary valvular regurgitation.[14] The "whippiness" of the pulmonary arterial curve, probably due to the proximity of the catheter tip to a site of turbulent flow, precluded identification of the dicrotic notch. The systolic gradient across the pulmonary valve might be due to a mild organic pulmonary stenosis with predominating regurgitation,[7] or, more likely, to a relative pulmonic stenosis. The systolic gradient across the pulmonary valve noted in this case has been described in both clinical and experimental pure pulmonary regurgitation.[8] This could be caused by a high velocity of flow through a pulmonary valve of normal cross-sectional area, as the right ventricle ejects the abnormally large stroke volume, consequent to the regurgitation. This phenomenon is also frequently encountered in association with the greatly increased total pulmonary flow in many cases of large intracardiac left-to-right shunt.

TABLE I. CATHETERIZATION DATA OF PATIENT R. A.

CATHETER LOCATION		BLOOD OXYGEN CONTENT (VOL. %)	BLOOD PRESSURE (MM. HG) SYSTOLIC/DIASTOLIC (MEAN)	
Inferior vena cava		10.4		
Superior vena cava		10.6		
Right atrium	high	11.8		
	mid	11.4		(7)
	low	11.3		
	low	11.4		
Right ventricle	apex	11.4	32/ 8	
	mid	11.4		
Main pulmonary artery		11.6	20/ 9	(15)
		11.4		
Right pulmonary artery		10.9	18/10	(15)
Right pulmonary artery wedge		14.1		(10)
Brachial artery	content	15.3	115/80	(90)
	capacity	16.3		
	saturation	95%		

Dye dilution curves (Figs. 5 and 6) confirmed the presence of pulmonic valvular regurgitation. The passage of T-1824 dye, following injection into various parts of the lesser circulation in rapid succession, was recorded by means of an ear oximeter. The dye curve following injection into a branch of the pulmonary artery beyond the apparent "sphere of influence" of the regurgitant valve was within normal limits. Dye curves following injections into the right atrium and ventricle were similar to each other, but demonstrated a lower peak concentration and a more prolonged rate of decline than was the case in the pulmonary arterial curve. The latter two dye curves were of a form characteristic of valvular regurgitation between the sites of injection and sampling of the dye.[15] This, with the normal dye curve from the pulmonary artery, localizes regurgitation to the pulmonary valve. The normal pulmonary arterial dye curve also rules out the presence of a left-to-right shunt, which deforms dye curves in a manner similar to valvular regurgitation.

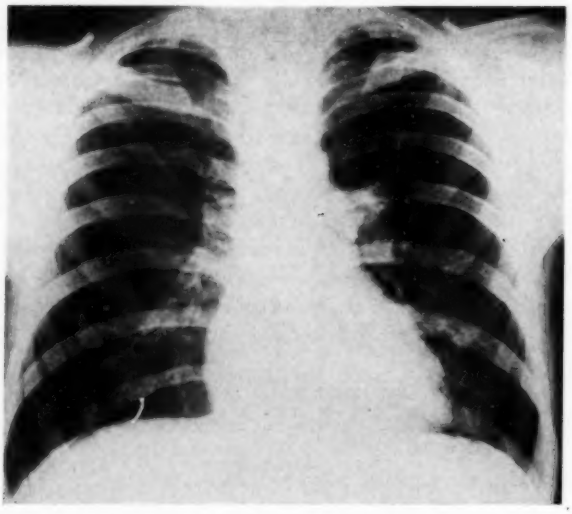


Fig. 1.—Posteroanterior teleroentgenogram of the chest. Note normal heart size and normal pulmonary vascularity. The pulmonary artery and its main branches are prominent.

DISCUSSION

Our 16-year-old patient had no symptoms referable to his pulmonic valvular regurgitation and led an active life which included highly competitive sports. A 7-year-old boy reported by Kjellberg and associates,[1] three children mentioned by Nadas,[4] and a 24-year-old medical student studied by Kezdi,[2] all were likewise asymptomatic. All were studied by cardiac catheterization. No shunts were demonstrated. Systolic pressure levels in the pulmonary artery and right ventricle were normal. All had below normal pulmonary arterial diastolic pressures approximating the right ventricular diastolic levels. The clinical picture, insofar as presented, resembled that of our patient. These cases comprise a group of asymptomatic young patients.

Morton and Stern[3] report a 20-year-old woman with typical clinical and catheterization findings of isolated pulmonic valvular regurgitation who was asymptomatic until her early teens, when mild, but persistent, symptoms of dyspnea, dizziness on exertion, and fatigability appeared. At rest, pulmonary

hypertension was absent and pulmonary vascular resistance was normal, as was the cardiac index. There was no apparent chronic pulmonary disease process, although acute episodes of "pleurisy" and pneumonia, respectively, occurred at age 15 and 20 years.

The diagnosis on all these patients was based on clinical and cardiac catheterization findings. The nature and size of the pulmonary valve defect remains unknown. Data on three additional patients, on whom surgical exploration or postmortem examinations were done, are also available. Brief reference to a 14-year-old boy who had been explored and found at surgery to have "destroyed pulmonary valves" is made by Ehrenhaft in discussing experimentally produced pulmonic valvular insufficiency.[8] This patient had had noted shortness of breath and decreased exercise tolerance since the age of 4 years. Reference is made to a cardiac catheterization study in which shunts were presumably not demonstrated, and which revealed a right ventricular pressure of 50/7 and a left pulmonary arterial pressure of 27/10 mm. Hg. Thus, a 20 mm. Hg systolic pressure gradient was present despite absent pulmonic valves.

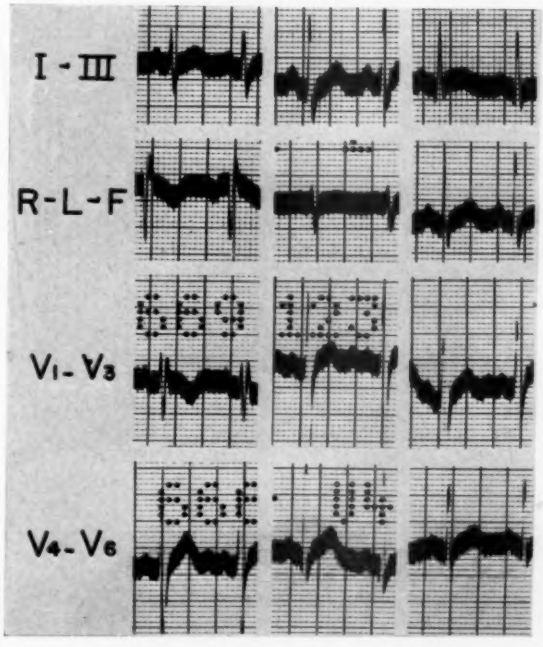


Fig. 2.—ECG suggestive of incomplete right bundle branch system block.

Another case report refers to a 46-year-old woman who had been asymptomatic until 43 years of age, and who then developed progressive exertional dyspnea, orthopnea, mild cyanosis on exertion, and severe right heart failure.[5] Cardiac catheterization studies revealed pulmonary systolic hypertension (75 mm. Hg), and greatly increased pulmonary vascular resistance, as well as right heart failure. The pressures in the pulmonary artery and right ventricle at end-diastole were equal, though elevated, as measured on the published curves. At

surgery for presumptive constrictive pericarditis (not present) a regurgitant jet from the pulmonic orifice was felt in the right ventricle during diastole. At autopsy the pulmonic valve was found to be bicuspid and malformed. Severe pulmonary emphysema and moderate pulmonary fibrosis, as well as pulmonary arteriosclerosis and hyaline necrosis, were also reported. A primary pulmonary disease process unrelated to the heart disease was considered to have produced the pulmonary hypertension, which, in turn, aggravated the pulmonary valvular regurgitation. The nature of this disease process is not evident. It is conceivable that the pulmonary changes may even have been secondary to the valvular lesion (see below).

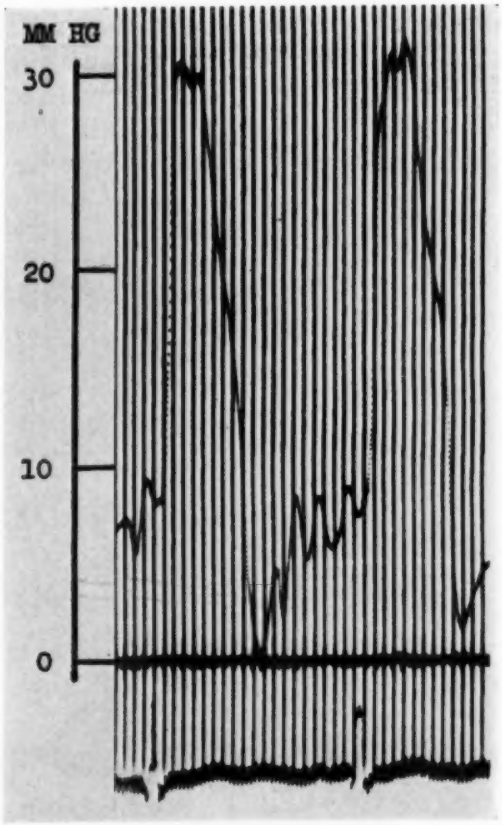


Fig. 3.—Right ventricular pressure curves at rest. Pressure levels are at the upper limits of normal.

Ford and associates[6] describe a patient with clinical and hemodynamic evidence of pulmonary valvular regurgitation with normal right ventricular and pulmonary systolic pressures at rest, who at autopsy was found to have a malformed bicuspid valve. This patient had been observed during a severe pulmonary tuberculosis infection which resulted in generalized pulmonary fibrosis. She developed dyspnea and signs of right heart failure, and died suddenly, presumably in ventricular fibrillation.

A cardiac catheterization study on a 45-year-old woman who, at age 18, acquired pulmonary regurgitation during a classical gonococcal endocarditis was reported by Olesen and Fabricius.[16] After a year of subacute infection the patient slowly recovered. At age 26, dyspnea on exertion was noted together with precordial pain; at age 42, right heart failure occurred. Normal right ventricular and pulmonary arterial systolic pressures at rest were noted. The diastolic pressure of the pulmonary artery was 0, as was that of the right ventricle.

Consideration of our case and the clinical reports in the literature permit a tentative conclusion that in youth an isolated, but dynamically significant, pulmonic valvular regurgitation is, as a rule, well tolerated. Since no long-term observations on individual patients are available, the prognosis of the lesion is uncertain. Morton's case suggests that symptoms may develop in patients with long-standing severe pulmonic valvular lesions in the absence of apparent complications. It would seem that "cardiac reserve" is reduced, and the additional burden imposed on the right ventricle by another disease process, such as pulmonary parenchymal disease, may lead more readily to right heart failure.

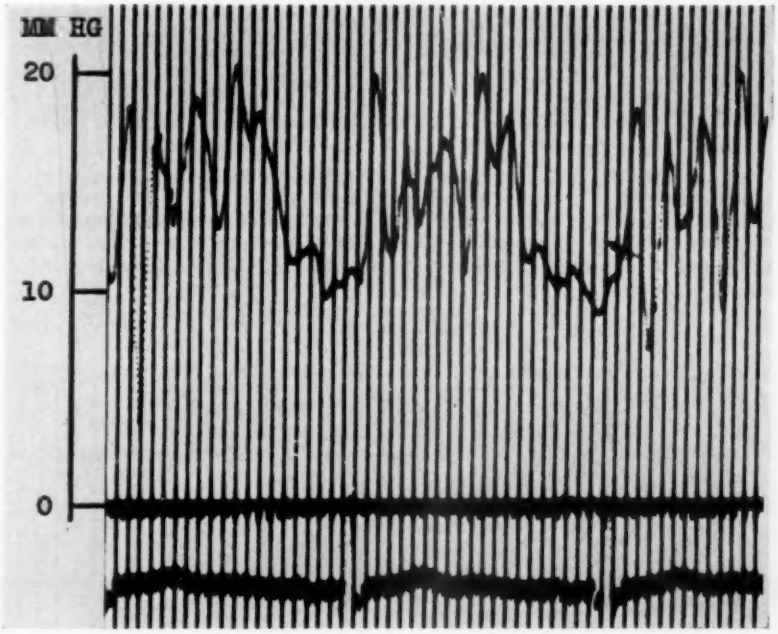


Fig. 4.—Main pulmonary arterial pressure curves. Note that the end-diastolic pressure is approximately that in the right ventricle, and that the dicrotic slope is steep. These two features are characteristic of dynamically significant pulmonic valvular regurgitation. The small systolic gradient between the right ventricle and pulmonary artery is discussed in the text, and does not necessarily imply that organic stenosis of the pulmonic valve is present.

Experimental studies involving the production of pulmonary valvular regurgitation in dogs lead one to conclude that a small defect is well tolerated without symptoms,[9,10] for many months at least. Induced pulmonary hypertension, in the presence of a small lesion, increases the regurgitation.[10] Other

experimental studies, however, suggest that a severe long-standing lesion might result in right heart failure without an additional disease process. Complete excision of the pulmonary valves in dogs resulted in definite right ventricular dilatation and hypertrophy.[11-13] The ratio of right ventricular to left ventricular heart weight was definitely increased in the study reported by Ratcliffe and asso-

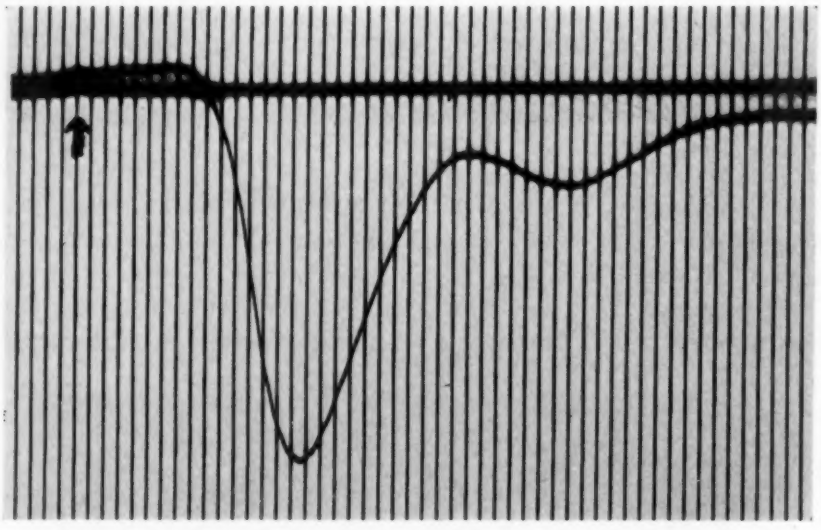


Fig. 5.—Normal dye dilution curve obtained by injecting, at the time indicated by the arrow, 15 mg. of Evans blue dye into a branch of the main pulmonary artery, with the catheter tip well beyond the pulmonic valve. Note the normal contour and clearly apparent recirculation of dye. Time lines are at 1-second intervals along the abscissa. The ordinate is proportional to the concentration of dye detected by an ear oximeter. Arrival time is 8 seconds, build-up time is 8 seconds, and disappearance time is 10 seconds.

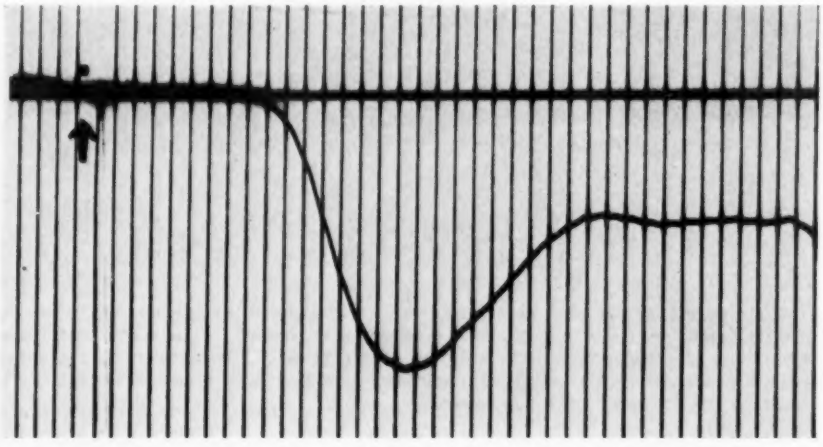


Fig. 6.—Dye dilution curve obtained by injecting 15 mg. of Evans blue dye into the right ventricle. It shows no significant difference in arrival and build-up times as compared to Fig. 5, but a significantly lower peak concentration of dye and a prolonged disappearance time. These features are characteristic of valvular regurgitation. Arrival time is 10 seconds, build-up time is 7½ seconds, and disappearance time is 15 seconds.

ciates,[12] in which 13 dogs were observed up to 10 months after total extirpation of the valves. Kay and Thomas[11] studied 15 dogs with total extirpation of the pulmonic valves and performed cardiac catheterization on them up to 27 months postoperatively. They did not report heart weights but found four greatly dilated right ventricles, and all others were dilated to a lesser degree. One of their dogs died of right heart failure after 8 months. Of considerable interest is their finding of right ventricular systolic hypertension. Ten dogs had systolic pressure greater than 50 mm. Hg, and in 3 cases it was above 90 mm. Hg. The dog that died of right heart failure had a pulmonary arterial pressure of 75/20 mm. Hg several weeks prior to death. Ten of the 13 dogs with total excision of the pulmonic valve reported by Kay and Thomas were found to have dilated pulmonary arteries and arterioles although no arteriosclerosis or medial hypertrophy had developed. It is probable that the latter changes could have occurred in the dogs with pulmonary systolic hypertension if they had lived long enough.

Hemodynamically, uncomplicated interatrial septal defect and uncomplicated absence of the pulmonic valve leaflet produce similar effects on the right ventricle, and one might anticipate a similar clinical course, leading to right heart failure, with or without pulmonary hypertension, in middle adult life.[17,18] If this train of events is eventually established by study of additional patients with dynamically significant valvular pulmonic regurgitation, two practical consequences become apparent. First, great care must be taken to avoid producing regurgitation during surgery for pulmonic stenosis; and secondly, surgery to construct competent pulmonic valves would be desirable in cases of isolated pulmonic valvular regurgitation in which the regurgitation is dynamically significant.

HEMODYNAMIC CONSIDERATIONS

The burden imposed on the heart by pulmonary valvular regurgitation is difficult to evaluate, although it must be a function of the amount by which stroke volume is increased secondarily to the regurgitation. It is known that the right ventricle can maintain an output many times the normal for many years without developing signs of failure, provided that the pulmonary arterial pressure remains normal. This is well documented in instances of interatrial septal defect in which the total pulmonary flow may be many times the normal value without concomitant pulmonary hypertension.[17] These clinical observations correlate well with recent animal studies showing that cardiac oxygen consumption does not increase to any great extent with marked increase in cardiac output, provided the blood pressure and heart rate remain constant.[19,20] Pulmonic valvular regurgitation increases the right ventricular stroke output by a variable amount which cannot be measured accurately by present methods in man. The amount of regurgitation will depend upon several factors: (1) cross-sectional area of the "diastolic orifice," (2) average diastolic pressure gradient between pulmonary artery and right ventricle, (3) pulmonary arterial distensibility, (4) pulmonary vascular resistance, (5) distensibility of the right ventricle, (6) duration of diastole, and (7) right ventricular stroke output.

1. *Cross-sectional area of the "diastolic orifice":* This refers to the valvular defect during diastole when the valves should occlude the pulmonic orifice. Clinical examples of possible extremes include total congenital absence of the pulmonic valves, on the one hand, and supernumerary valves which almost occlude the pulmonic orifice during diastole, on the other. Partial removal of one or two pulmonary cusps in dogs did not acutely abolish the end-diastolic gradient between the pulmonary artery and right ventricle, but insertion of a wide glass tube in such a position as to prevent closure of the valves did have this effect in the same animal.[10] These facts suggest that regurgitant flow is increased by an increased diastolic orifice. Further support is provided by experiments in which excision of all the pulmonic valve cusps in 15 dogs led to right heart failure in one, marked right ventricular dilatation in four, and definite right ventricular dilatation in all.[11]

2. *Average diastolic pressure gradient between pulmonary artery and right ventricle:* Pulmonary hypertension associated with increased pulmonary vascular resistance will greatly increase this gradient, and numerous clinical and experimental studies emphasize the importance of this factor.[10]

3. *Pulmonary arterial distensibility:* Regurgitant flow ultimately takes place only as a consequence of potential energy stored in the pulmonary arterial wall as it is distended during ventricular systole by the blood ejected from the right ventricle. During ventricular diastole the distended pulmonary arterial system contracts, driving the blood forward, and in the presence of incompetent pulmonic valves, backward. Were the arteries completely nondistensible, potential energy would not be stored and regurgitation would be minimal. Thus, it is evident that the elasticity characteristics of the pulmonary vessels must be included among the factors which determine the amount of regurgitant flow.

4. *Pulmonary vascular resistance:* Augmentation of this resistance slows the rate of peripheral runoff of blood through the capillary bed for any given pulmonary arterial pressure level. This results in increased end-systolic distension of the pulmonary arteries and, therefore, in increased regurgitation. On the other hand, were ventricular ejection exactly equaled by the rate of forward flow into the pulmonary capillaries because of low vascular resistance, minimal pulmonary arterial distension would occur and, hence, regurgitant flow would be reduced.

5. *Distensibility of right ventricle:* If the pulmonary valvular diastolic orifice is sufficiently large, the distribution of a given right ventricular stroke output will depend on two competing factors, namely, the right ventricular distensibility governing regurgitant flow, and the pulmonary vascular resistance governing forward flow. The importance of the "suction effect" of the relaxing ventricle has not yet been demonstrated in man.[21]

6. *Duration of diastole:* This is a function of heart rate. Wiggers[22] deduced that in small aortic valvular leaks one third of the regurgitant flow occurs in protodiastole, as opposed to two thirds when the aortic leak is large. If similar conditions obtain in pulmonary regurgitation, then increased heart rate will reduce regurgitant flow by decreasing diastolic duration, and this reduction will be more marked when the pre-existent leak is small than when it is large.

7. *Right ventricular stroke output:* If all other factors remain constant, an increase in right ventricular stroke output will result in greater end-systolic distension of the pulmonary artery. Pulmonary arterial end-systolic pressure will be correspondingly elevated. An augmented early diastolic pressure gradient between the pulmonary artery and right ventricle will result, and pulmonic valvular regurgitation will be relatively increased. In the absence of heart failure, right ventricular stroke output is increased by increased venous return[23]; therefore, any factor increasing venous return will tend to increase pulmonic valvular regurgitation.

The size of a regurgitant flow is important insofar as it affects cardiac effort. The existence of regurgitation implies considerable turbulence of flow. Consequently, the ideal steady state of streamline flow assumed in calculation of cardiac external work is deviated from greatly.[24] The abrupt variations of "pipe" diameter, and the numerous short vascular branches characteristic of the pulmonary arterial tree, the pulsatility of ejection and pressure, all normally predispose to turbulence. In valvular regurgitation, the cyclic reversals of flow direction which take place will further enhance the production of eddy currents and turbulence. Since the increased stroke volume due to regurgitation is not accompanied by a proportional increase in duration of right ventricular systole, the velocity of ejection will be greatly increased. This will not only increase the turbulence but also the kinetic energy of flow. These latter two factors, ordinarily negligible as compared to the energy expenditure of pressure work, may in the presence of greatly increased stroke volume and regurgitation represent a considerable waste of energy and may become relatively quite important.[25]

Large regurgitant flows not only greatly increase stroke volume but also, in many instances, lead to ventricular dilatation during diastole. Recent theoretical considerations[26] have suggested that cardiac muscle work is increased by increased cavitary volumes because of the added muscle fiber tension needed to build up the same intracavitary pressure during systole. In addition, marked dilatation of the right ventricle may result in tricuspid regurgitation, which will further increase the burden imposed on the right heart.

CONCLUSION

Thus, it is apparent on clinical, experimental, and theoretical grounds that pulmonic valvular regurgitation of sufficient dynamic significance could of itself result in clinical disability and heart failure. Furthermore, even in the absence of symptoms, the innocence of such lesions should not be assumed. Long-term observation of many asymptomatic patients will be necessary to support the generally assumed innocence of such lesions.

We are grateful to Dr. Ernest Mond for permission to report this case, and to Dr. Louis N. Katz for much helpful advice and criticism.

REFERENCES

1. Kjellberg, S. R., Mannheimer, E., Rudhe, U., and Jönsson, B.: Diagnosis of Congenital Heart Disease, Chicago, 1955, The Year Book Publishers, Inc., pp. 516-517.

2. Kezdi, P., Priest, W. S., and Smith, J. M.: Quart. Bull. Northwestern Univ. Med. School **29**:368, 1955.
3. Morton, R. F., and Stern, T. N.: Circulation **14**:1069, 1956.
4. Nadas, A. S.: Pediatric Cardiology, Philadelphia, 1957, W. B. Saunders Company, pp. 483-486.
5. Dickens, J., Raber, G. T., and Goldberg, H.: Ann. Int. Med. **48**:851, 1958.
6. Ford, A. B., Hellerstein, H. K., Wood, C., and Kelly, H. B.: Am. J. Med. **20**:474, 1956.
7. Donzelot, E., and D'Allaines, F.: Traité des Cardiopathies Congénitales, Paris, 1954, Masson et Cié., p. 383.
8. Ellison, R. C., Brown, W. J., Hague, E. E., Jr., and Hamilton, W. F.: J. Thoracic. Surg. **30**:633, 1955.
9. Barger, A. C., Roe, B. B., and Richardson, G. S.: Am. J. Physiol. **169**:384, 1952.
10. Fowler, N. O., Mannix, E. P., and Noble, W.: Circulation Res. **4**:8, 1956.
11. Kay, J. H., and Thomas, V.: A.M.A. Arch. Surg. **69**:646, 1954.
12. Ratcliffe, J. W., Hurt, R. L., Belmonte, B., and Gerbode, F.: Surgery **41**:43, 1957.
13. Fowler, N. O., and Duchesne, E. R.: J. Thoracic Surg. **35**:643, 1958.
14. Kohout, F. W., and Katz, L. N.: Am. Heart J. **49**:637, 1955.
15. Woodward, E., Jr., Burchell, H. B., and Wood, E. H.: Proc. Staff Meet. Mayo Clin. **32**:518, 1957.
16. Olesen, K. H., and Fabricius, J.: Am. Heart J. **52**:791, 1956.
17. Dexter, L.: Brit. Heart. J. **18**:209, 1956.
18. Muller, W. H., Jr., Smith, S. W., Dammann, J. F., Jr., Adams, F. H., and Darsie, M. L.: Surgery **37**:1, 1955.
19. Alella, A., Williams, F. L., Bolene-Williams, C., and Katz, L. N.: Am. J. Physiol. **183**:570, 1955.
20. Laurent, D., Bolene-Williams, C., Williams, F. L., and Katz, L. N.: Am. J. Physiol. **185**:355, 1956.
21. Brecher, G. A., and Kissen, A. T.: Circulation Res. **6**:100, 1958.
22. Wiggers, C. J.: J.A.M.A. **97**:1359, 1931.
23. Katz, L. N.: Physiol. Rev. **35**:91, 1955.
24. Prec, O., Katz, L. N., Sennett, L., Rosenman, R. H., Fishman, A. P., and Hwang, W.: Am. J. Physiol. **159**:483, 1949.
25. Landowne, M., and Katz, L. N.: Circulatory System: Heart; Work and Failure, Medical Physics, Vol. II, Chicago, 1950, Year Book Publishers, Inc., pp. 194-206.
26. Burton, A. C.: Am. Heart J. **54**:801, 1957.

Review

The Digital Circulation

Milton Mendlowitz, M.D., New York, N. Y.

INTRODUCTION

Study of circulation through small blood vessels has interested many investigators over the past years, largely because local circulations differ from one another, in harmony with differences in function of the organs irrigated. It has also become apparent gradually that the circulation in general is controlled in large measure by the resultant of factors influencing each local circulation. Clinicians, however, have hesitated to adapt such studies to the routine investigation of disease in the individual patient, since the methods are often complicated and expensive and their immediate practical value for therapy frequently not established. Small inroads have been made against this justifiable resistance, especially where surgical procedures demand more exact information than is ordinarily clinically available, but it is unusual for the clinician to ask for studies on the pulmonary, renal, hepatic, or even the peripheral circulation, except for such special purposes.

Circulation through an extremity and especially through a digit, on the other hand, is so accessible and is measured by techniques comparatively so simple that here, if anywhere, it might be possible to glean information of general clinical usefulness, in addition to the special information needed in connection with localized disease. Thus, one might use such techniques not only for the investigation of disease localized to the digits, but also for the study of circulatory changes during anesthesia or in hypertension or shock. It is the purpose of this review to analyze critically the current status of such studies with regard to these objectives and to point out, if possible, the direction they may take in the future.

METHODS

As is usual in such developments, the question of method is interlaced in a complex manner through the entire body of research in this field. Attention

Aided by grants from the American Heart Association and the National Heart Institute (H-1164).
Received for publication Oct. 27, 1958.

has been focused particularly on the measurement of digital blood pressure, blood flow, and the state of the digital blood vessels themselves.

Blood Pressure.—Methods for measuring digital blood pressure have evolved progressively since the time of Gaertner.[1] He proposed his digital capsule for the general measurement of blood pressure before the Riva-Rocci cuff[2] became popular. The original Gaertner capsule was a circular metallic band about one inch in width, lined with a rubber membrane which could be inflated through a side tube in the band, pressure being measured by an interposed mercury manometer. Digital systolic pressure was measured after blanching the finger by rolling a rubber band from tip to base and then inflating the capsule to a point above systolic pressure. After cutting the rubber band, the capsule was then gradually deflated until flushing appeared in the finger tip. At this point, which was slightly below systolic pressure, jets of blood could get through the artery, and since the veins were obstructed, the finger reddened and became congested. It soon became apparent, however, that digital arterial blood pressure fluctuated more than brachial arterial pressure; and since, in addition, Gaertner presented no objective method for measuring diastolic pressure, the Riva-Rocci cuff and the Korotkow sounds[3] came into general use for the indirect measurement of blood pressure in man. The Gaertner capsule was forgotten, only to be revived sporadically by investigators interested in special problems. Cohn and Lundsgaard[4] used it to study blood pressure in auricular fibrillation in 1918; whereas Formijne,[5] in 1934, was interested in the patency of large arteries, and in 1937, Oppenheimer and Prinzmetal[6] studied the brachial-digital pressure gradient in hypertension.

In 1938,[7] I became interested in brachial-digital pressure gradients while working on the problem of the mechanism of clubbing of the fingers under the direction of Sir Thomas Lewis, in London, and again used the Gaertner capsule to measure digital arterial pressure. Systolic pressure was measured by the usual flushing technique. As the capsule was deflated, however, a sensation of throbbing was usually felt in the finger. This began slightly above true systolic pressure as measured by the flush, because blood would come through the proximal edge of the cuff only, where tissue pressure was lower than cuff pressure, but not through the entire cuff. The throbbing then stopped suddenly at a pressure level consistent with that of the diastolic pressure. I found that von Recklinghausen[8] had compared diastolic pressure as measured from the cessation of throbbing under the cuff in the arm to that measured from the muffling of the Korotkow sounds and had found them to be nearly identical. It therefore seemed safe to consider the pressure at the point of cessation of throbbing in the digit to be diastolic digital arterial pressure.

Meanwhile, the capsule itself was being modified. Formijne[5] and also Oppenheimer and Prinzmetal[6] had suggested that it be slightly tapered in order to fit the finger better, and that three or four different sizes of capsules be available. The appropriate one could then be chosen for a given finger so that the fit would be snug but not obstructively tight. I later found the results to be just as good if the capsule were not tapered.[9] Grooves were ground in the capsule so that Penrose tubing could be made to line it and be fastened over the

edges easily with rubber bands. Weaver and Bohr,[10] however, devised a miniature Riva-Rocci cuff for the finger with cloth backing, and Brecht and Boucke[11] developed a similar cuff with very thin metal backing which could be adjusted to various finger sizes.

In addition, the search continued for better methods for measuring digital arterial blood pressure with these devices. The capillaries of the eponychium were visualized with the capillary microscope at various cuff pressures by Davis,[12] although he did not realize that he was measuring digital arterial systolic pressure rather than some function of capillary pressure. Doupe, Newman and Wilkins[13] and also Wishart[14] used the plethysmograph, and Lax, Feinberg and Cohen,[15] the oscillograph, to measure systolic pressure by picking up pulsations distal to the pressure cuff and recording these pulse waves either photographically or with a thermal stylette. These waves could also be harnessed to record systolic blood pressure continuously.[13] Moreover, Lax, Feinberg and Cohen[15] pointed out a change in the diastolic portion of the pulse curve as arterial blood pressure reached the diastolic level, which they called the "diastolic sign," and they could therefore record systolic as well as diastolic pressure by a double-cuff technique.

Meanwhile, Eurman and I[16] made abortive attempts to hear Korotkow sounds in the finger. We tried electronic sound pickups unsuccessfully, and finally used Fox localizers on stethoscopes with metallic diaphragms and could often hear the sounds directly over the volar digital arteries. These were not heard consistently, however, in all individuals, especially during extreme vasoconstriction. Using two diaphragms, each one connected to one ear, we could occasionally detect differences in pressure between the two volar digital arteries and identify an auscultatory gap. In 1958, Gaskell and Krisman[17,18] described a simple device for detecting Korotkow sounds; it consisted of a glass capsule surrounding the finger tip and bound down to the second phalanx with elastoplast adhesive tape. A stethoscope was attached via a tube to the glass capsule. The sounds were heard quite distinctly except in small or in very cold fingers, and systolic and diastolic pressures could be measured by auscultation. They also tested the effect of the length of the occluding cuff on the estimation of blood pressure and found that it should be at least one and one-eighth inches long in order to record blood pressure in the digits correctly. In addition, they tested the auscultatory, plethysmographic, and capillaroscopic methods for measuring systolic pressure against each other and found that they checked fairly well. Meanwhile, we[19] had acquired a device for oscillographic visualization and recording of Korotkow sounds in the digits with a capacitance pickup as devised by Brecht and Boucke.[11] Both systolic and diastolic pressures as measured by the flushing and throbbing techniques were determined simultaneously with pressures measured from these visualized Korotkow sounds, and again checked fairly well. Green[20] used this device to record blood pressure continuously from a digit, the appearance of the pulse wave with deflation of the cuff being used to trip reinflation of the cuff electronically. A similar setup has been used for recording pressures continuously during anesthesia, thus monitor-

ing the dose of the anesthetic administered.[21] As far as capillary pressure is concerned, the only reliable method is the exacting direct-puncture technique of Landis.[22] Venous pressure in the digit can also be studied now with the Burch-Winsor small needle phlebomanometer.[23]

As the situation stands today, the two simplest devices for measuring digital arterial blood pressure are the flushing-throbbing method and the auscultatory method using the Gaskell-Krisman capsule. Both are reliable when checked against more exacting techniques, and both may fail if the fingers are very cold or small, although the flushing-throbbing technique fails less often under these circumstances. Precaution should be taken to have a cuff which is long enough and which is adjustable to the circumference of the finger. On the average[18] the systolic pressure is 18.5 mm. Hg, and the diastolic pressure 12.1 mm. Hg, lower than the corresponding brachial arterial pressures when the subject is warm, whereas capillary pressures are on the average 43.5 cm. in the proximal and 16.5 cm. of water in the distal limb of the loop.[22] Digital venous pressure at heart level is on an average 14 cm. of water.[24]

Blood Flow.—Methods have also been developed concomitantly for measuring blood flow in the digits. In general, these methods have been either plethysmographic or thermal. The plethysmograph is an old physiologic device for measuring the volume of an organ, hence its arterial inflow during venous obstruction, as exemplified by the renal oncometer. It was first used in man for this purpose by Hewlett and Van Zwaluwenberg,[25] in the arm. It began in 1933 and thereafter to be used to measure digital blood flow by workers such as Goetz,[26] Turner, Burch and Sodeman,[27] Burton,[28] Wilkins, Doupe and Newman,[29] and Megibow and Feitelberg,[30] among others. Molitor and Kniazuk,[31] Hertzman,[32] and Gross, Matthes and Göpfert[33] were some of the workers who developed and studied the properties of a photoelectric digital plethysmograph. Horeman[53] also studied application of the mercury strand plethysmograph to the digit, and although the findings with all such instruments, including the impedance plethysmograph, bear a rough relationship to the results with true volume recorders, the latter are generally the most reliable, especially for measurement of absolute blood flow and comparison between different patients. The relative technical merits of liquid-in-tube recorders and membrane volume recorders with reference to frequency response and fidelity of recording need not be discussed here, except to say that such factors must always be considered when an instrument is chosen.[53]

Several studies[28,53] have shown that there is a proportion between pulse volume and blood flow, and although this is useful for studying changes in flow in individual subjects, it cannot be adapted for quantitative comparisons between subjects. For this purpose, increase in volume with venous occlusion is usually employed.

Although this procedure is theoretically sound, several practical difficulties began to appear as it was used. For one thing, the method measured flow intermittently rather than continuously and required careful attention to detail. There were errors attributable to leaving a gap between the occluding cuff and the plethysmograph. Moreover, especially when this gap was eliminated, there was an artefact due to the compression of tissue into the plethysmograph by

the occluding cuff,[34] the accumulation of lymph, and other factors. The occluding cuff itself could set off neurogenic reflex vasoconstriction in the sensitive digital blood vessels.[35] Also, the capacity of the venular bed in the digit was small for the amount of blood coming into it,[36] and pressure rather than volume quickly became the predominant parameter to change with inflow. This effect was exaggerated by venular constriction produced by a cold environment. With indirect heat, on the other hand, the inflow was so great and the slope of the volume change so steep that it was difficult to be sure of the quantitative flow.[34] There was also the nagging fear that a small leak via the bones could bypass the occluding cuff and, hence, give an erroneous idea of the volume change,[35] although this appears now to be unlikely, at least immediately after venous occlusion.[53] In obstructive arterial disease, moreover, it is possible to set the pressure of the occluding cuff higher than digital arterial diastolic pressure, thus interfering with inflow.[37]

These considerations motivated Burch[34] to measure pulse volume continuously and to subtract electronically an artefact and inflow pulse wave as determined after venous occlusion. Thus, the results could be converted electronically into measurement of outflow both instantaneously and per unit time. Despite the complex instrumentation this technique will undoubtedly find its place after comparison with other devices for measuring digital blood flow, and may in its present form, or after modification, serve as a yardstick for this purpose.

Apart from measurement of blood flow, however, the plethysmograph as well as the oscillograph serve well-defined purposes. They are sensitive continuous volumetric recorders, and five different types of wave formations have been described.[38] Vascular reflexes and even conditioned reflexes[39] may be nicely demonstrated plethysmographically. Change in the contour of the pulse wave is easily detected by either the plethysmograph or the oscillograph and may identify certain diseases,[15,30,40,41] such as aortic insufficiency, coarctation of the aorta, or arteriosclerosis. The plethysmograph or oscillograph may also be used in conjunction with other techniques already mentioned to measure digital arterial blood pressure.

Thermal measurement of digital blood flow has also had a long and checkered career. The relationship between cold hands and ischemia was recognized by clinicians for many years, but it was not until thermoelectric measurements became available that the subject was studied intensively.[42-44] It soon became clear that there was a rough correlation between skin temperature and blood flow, especially in the digits, and the reason for this was found to reside in the adaptation of the peripheral circulation to the regulation of body temperature. The arteriovenous anastomoses of the digits could convey a large quantity of blood per unit time, and if the body were in positive heat balance, could thus eliminate considerable thermal energy through the overlying skin. Conversely, if the body were in negative heat balance due, for example, to excessive loss of heat because of cold, the arteriovenous anastomoses, which were under adrenergic or sympathetic nervous control, could close down and the fingers and toes would become cold because of extremely decreased blood flow. It was also apparent, however, that skin temperature would be influenced not only by rate of blood

flow but also by ambient room temperature and by the temperature of the arterial blood. Burton[45] worked out a formula for quantification of blood flow from all these factors, which he called a thermal circulatory index, but although again useful for measuring changes in circulation in an individual patient, this index could not very well be made sufficiently quantitative for comparison between patients, and this is generally true of all skin temperature measurements.[9,46] What is worse, however, is that the relationship between skin temperature and blood flow is not rectilinear. This can be understood when one realizes that no matter how much blood is flowing through the skin per unit time, skin temperature cannot at ordinary ambient temperatures be raised any higher than blood temperature. At a skin temperature of 36°C., therefore, doubling or trebling the blood flow would change the temperature very little, if at all.[9,47]

It was G. N. Stewart[48] who first discovered that the Fick principle could be applied to circulation through the extremities, heat rather than oxygen being the measured parameter. He reasoned that if the number of calories elaborated by an extremity per unit time could be measured, and if the arteriovenous temperature difference were known, the blood flow could be calculated. Thus, if two grams of arterial blood came to the skin in a minute at a temperature of 37°C. and left the skin in venous blood at a temperature of 31°C., twelve calories by definition would be lost. If these calories could be picked up in a calorimeter and divided by the arteriovenous temperature difference, which in this case would be 6°C., one would arrive at the blood flow of two grams per minute.

The principle was sound, but the assumptions he made were not. He devised a water calorimeter to pick up the caloric output of the hand or foot, and decided that average calorimeter temperature would represent the temperature of the venous blood, and mouth temperature, the temperature of the arterial blood. Unfortunately, in the hand, much of the blood flow comes from the deep veins and remains uncooled in a water calorimeter, so that direct measurement of venous blood temperature reveals it to be variably higher than calorimeter temperature.[49] What is more, arterial blood temperature can be considerably decreased in very cold environments, so that it is variably lower under these conditions than mouth temperature.[50]

In the finger, however, most of the circulation is through the arteriovenous anastomoses of the skin, and Stewart's assumption that venous blood temperature is equal to calorimeter temperature holds very well.[51] The equivalence between mouth and arterial blood temperature, however, holds only if room temperature is at 26°C. or above.[52] Therefore, it is best when doing calorimetry to keep room temperature between 26° and 29°C. Horeman,[53] in a brilliant mathematical analysis in which he critically examined calorimetry and compared it with plethysmography, felt that caloric output per volume of finger tip gave values for blood flow about 35 per cent too low as a consistent factor. The true values of some of his mathematical constants, however, have not been unequivocally established, and his comparative measurements were not made simultaneously. Deep blood flow, moreover, which is about 10 per cent of total flow in the digit, is not measured by any calorimeter. Also, room temperature in his experiments was often 22°C., so that axillary temperature which he took

to represent arterial blood temperature was probably higher than the true arterial blood temperature. These factors will have to be considered in future experiments and judgment on correspondence suspended until then.

As to instrumentation, the first digital calorimeter which I designed[7] was similar to Stewart's hand calorimeter. It was a simple aluminum cup filled with water and set in broken cork. It contained a hand stirrer and a Beckmann thermometer; and a rubber membrane with appropriate apertures covered the top. As time went on, Greenfield and Shepherd[36] added a heating device to counteract the effect of room temperature, and I also used one of a slightly different character.[54] I also used a Dewar flask instead of an aluminum cup, and went, in sequence, from a hand stirrer to a rotary motor-driven glass stirrer to an electromagnetic stirrer.

Hensel,[55,56] meanwhile, had developed a flow calorimeter based on differential temperature between outflowing and inflowing water continuously recorded electrically. He used a plastic capsule for picking up heat from the skin, rather than direct contact with the water, and his values were therefore too low in general. Horeman[53] developed a direct water contact flow calorimeter based on principles developed by Hensel[55,56] and also by Aschoff.[57] In the meantime, an entirely different type of calorimeter based on the rate of evaporation of a fluid at a specific temperature was developed by Barany.[58] This had the advantage of being applicable to any region of the skin. It also was extremely simple but left some doubt about "border" effects at the edge of the area of application of the calorimeter. The same question, as well as the question of adequacy of contact, applies to disc and thermopile calorimeters,[56,59,60] although Hensel and Bender were able to demonstrate a rectilinear relationship between caloric output and blood flow with such an instrument.[56] Meanwhile, Feitelberg and I[61] developed a continuously recording calorimeter or blood flow meter based on heat balance within a thermal sink.

To sum up, blood flow can be measured with the digital plethysmograph by venous occlusion, provided the observer is aware of the technical limitations of the particular apparatus and method he uses. The pulse volume serves as a rough index of blood flow changes in an individual subject. Blood flow can also be measured with a variety of thermal devices, all of which measure caloric output from the skin. This can be continuously recorded best by either a flow calorimeter or a thermal sink calorimeter, and if room temperature is kept between 26° and 29°C., can be calibrated in terms of blood flow. Disc calorimeters are simpler and more flexible but their accuracy requires further testing. Skin temperature is a rough index of blood flow in the digit only between certain limits[47] (approximately 23° to 32°C.). All thermal devices have a lag varying between a few seconds and several minutes, and therefore only measure mean blood flow in a relatively steady state. They only record mass (slow period) changes in blood flow. All such devices also require small correction factors for specific heat and specific gravity of blood.[9,62]

Blood Vessels.—The state of the digital blood vessels can be observed in several ways. Arteriography[63] can delineate the digital arterial system radiographically. Capillaroscopy[64-68] can make the loops in the eponychium visible,

and for more accurate recording these can be photographed. Although a literature has been built up on changes in the capillaries caused by disease, one must be careful not to be misled by local factors.

Knowledge of the anatomy and histology of the digital circulation, moreover, is being developed continuously. The description of the Sucquet-Hoyer canals[69,70] and their intense study by Grant[71,72] as well as by Popoff,[73] and Masson and Géry's[74] study of these structures and of glomangiomata are of continuing importance. Even very recently, Burch and Phillips confirmed the presence in the digital skin of a cell containing chromaffin granules and presumably capable of elaborating vasoconstrictor substances locally.[75,76] Also, Lovell[77] described digital vascular changes in detail in histologic studies of clubbed fingers.

Moreover, the entire subject of indirect measurement of vasomotor tone has been developed in man in the digits. The relationship between pressure and flow worked out in animals in relation to viscosity by Whittaker and Winton,[78] and in relation to vasomotor tone by Pappenheimer and Maes,[79] Green, Lewis, Nickerson and Heller,[80] and Nichol, Girling, Jerrard, Claxton and Burton[81] have all been applied to the digital circulation of man. I measured changes in the flow-pressure slope with changes in blood viscosity in the digit.[82] Yamada and Burton, I, Torosdag and Sharney, and later Gaskell and Krisman all studied critical closing pressure of blood vessels in the digits, both in normal and hypertensive subjects.[83-87] There are some discrepancies because of differences in approach and in method, but all workers are agreed that the critical closing pressure is higher in hypertensive than in normotensive subjects, although we find[84,86] that the difference disappears with vasodilatation, since critical closing pressure approaches zero in both groups under these conditions. We have also worked out a procedure for estimating the pressure axis intercept of the pressure-flow slope, which includes the factor of critical closing pressure and/or viscosity change with vasoconstriction, from any given flow-pressure ratio.[84,87]

In addition, we have devised a method for converting flow-pressure ratios into measurements of radius equivalents of the digital circulation by applying Poiseuille's law to a single tube equivalent of the circuit, thus abandoning the term "peripheral resistance" entirely.[84] From the pressures and radius equivalents, moreover, the physical work and force of vasoconstriction can be measured. It is only by means of measurements of this kind that vasomotor tone can be compared quantitatively between different groups, as, for example, normotensive and hypertensive.

APPLICATIONS

Now what is the meaning of all this in terms of disease, and how has it added to out knowledge? This is already incalculable. Part of the mechanism of acquired clubbing of the fingers, for example, has been elucidated.[7,9,88] The extreme degree of arterial obstruction that must occur before any symptoms of ischemia become apparent is now clear.[9] It has been shown that neurovascular change in the toes is one of the earliest measurable manifestations of vascular disease in diabetes mellitus.[58,89,90] Increased sensitivity to norepinephrine has

been clearly demonstrated in primary hypertension[91] and in Cushing's syndrome,[92] suggesting that adrenal cortical steroids inhibit the enzyme in vascular smooth muscle which is responsible for the degradation of norepinephrine, and that primary hypertension is caused by a deficit in this enzyme. Continuous measurement of pressure or flow in the digital circulation gives promise of serving as a monitor for changes in cardiac output during the course of anesthesia.[9] The complex effects of sympathectomy on the circulation have been carefully and thoroughly evaluated.[93,94] These are only a few of the general dividends of this investment.

Is there anything of practical importance for the individual patient in all of this as yet? Actually, very little! It is important, for example, that all patients with Raynaud's disease should be studied by testing flow and pressure and even by arteriography[95] if necessary, since there are two types, one with vascular obstruction and one without such obstruction but with increased vasomotor tone.[96] What is more, two similar abnormalities, that is, vascular obstruction and neurogenic vasospasm, can be differentiated in patients without Raynaud's spasms but with what has been labeled acrocyanosis.[95,97] The prognosis and even the treatment to some extent is affected by accurate diagnosis here.

It is also important to measure circulatory changes before and after surgical procedures involving the arterial tree.[98,99] It is possible for pulse pressure to be increased without any increase in flow, and the success or failure of a surgical procedure can and should be documented by accurate circulatory measurements.

Although some correlation can be established between response to therapy in hypertension and digital circulatory changes, and also between the stage of the disease and such changes,[100,101] the correlation is not good enough as yet for prediction or prognosis in the average individual case. Some useful information, however, such as the extent of the neurogenic factor, can often be garnered. In the second trimester of pregnancy,[102] however, increased sensitivity to norepinephrine seems to be well correlated with the subsequent development of "toxemia." Biopsy of the digital skin blood vessels may reveal changes of importance in diagnosis and therapy, although this is still in the developmental stage.[75] In addition, the effect of drugs on peripheral vessels has been studied by many investigators.[9,103,104] Practical applications are therefore developing and together with theoretical implications will undoubtedly slowly multiply.

REFERENCES

1. Gaertner, G.: Wien. klin. Wchnschr. **12**:696, 1899.
2. Riva-Rocci, S.: Gaz. Med. di Torino **47**:98, 1896.
3. Korotkow, S.: Izvest. imp. Voyenno-Med. Acad. St. Petersburg **11**:365, 1905.
4. Cohn, A. E., and Lundsgaard, C.: J. Exper. Med. **27**:487, 1918.
5. Formijne, P.: Am. Heart J. **10**:1, 1934.
6. Oppenheimer, E. T., and Prinzmetal, M.: Arch. Int. Med. **60**:772, 1937.
7. Mendlowitz, M.: Clin. Sc. **3**:387, 1938.
8. Von Recklinghausen, H.: Arch. f. exper. Pathol. u. Pharmakol. **55**:375, 1906.
9. Mendlowitz, M.: The Digital Circulation, New York, 1954, Grune & Stratton, Inc.
10. Weaver, J. C., and Bohr, D. F.: Am. Heart J. **39**:413, 423, 1950.
11. Brecht, K., and Boucke, H.: Pflüger's Arch. f.d. gesamte Physiologie **256**:43, 1952-3.
12. Davis, E.: A.M.A. Arch. Int. Med. **91**:715, 1953.
13. Doupe, J., Newman, H. W., and Wilkins, R. W.: J. Physiol. **95**:244, 1939.

14. Wishart, G. M.: Clin. Sc. **1**:159, 1933.
15. Lax, H., Feinberg, A. W., and Cohen, B. M.: J. Chron. Dis. **3**:48, 1956.
16. Eurman, G. H., and Mendlowitz, M.[9]
17. Gaskell, P., and Krisman, A. M.: Canad. J. Biochem. and Physiol. **36**:883, 1958.
18. Gaskell, P., and Krisman, A. M.: Canad. J. Biochem. and Physiol. **36**:889, 1958.
19. Mendlowitz, M., and Naftchi, N.: Unpublished data.
20. Green, J. H.: J. Physiol. **130**:37, 1955.
21. Gilford, S. R., and Broida, H. P.: National Bureau of Standards, Report #3301, 1954.
22. Landis, E. M.: Heart **15**:209, 1929.
23. Burch, G. E., and Winsor, T.: J.A.M.A. **123**:91, 1943.
24. Ochsner, A., Jr., Colp, R., Jr., and Burch, G. E.: Circulation **3**:674, 1951.
25. Hewlett, A. W., and Van Zwaluwenberg, J. G.: Heart **1**:87, 1909.
26. Goetz, R. H.: Pflüger's Arch. f.d. gesamte Physiologie **235**:271, 1935.
27. Turner, R. H., Burch, G. E., and Sodeman, W. A.: J. Clin. Invest. **16**:789, 1937.
28. Burton, A. C.: Am. J. Physiol. **127**:437, 1939.
29. Wilkins, R. W., Doupe, J., and Newman, H. W.: Clin. Sc. **3**:403, 1938.
30. Megibow, R. S., and Feitelberg, S.: Am. J. Med. **4**:798, 1948.
31. Molitor, H., and Kniazuk, M.: J. Pharmacol. & Exper. Therap. **57**:6, 1936.
32. Hertzman, A. B.: Am. J. Physiol. **124**:328, 1938.
33. Gross, F., Matthes, K., and Göpfert, H.: Klin. Wchnschr. **19**:73, 1940.
34. Burch, G. E.: Digital Plethysmography, New York, 1954, Grune & Stratton, Inc.
35. Mendlowitz, M., Touroff, A.S.W., and Abel, H. A.: J. Clin. Invest. **30**:94, 1951.
36. Greenfield, A. D. M., and Shepherd, J. T.: Clin. Sc. **9**:323, 1950.
37. Matthes, K.: Third World Congress of Cardiology, Brussels, Abstract of Symposia, 269, 1958.
38. Burch, G. E., Cohn, A. E., and Neumann, C.: J. Clin. Invest. **21**:655, 1942.
39. Winsor, T., Selle, W. A., and Mavardi, Y. K.: A.M.A. Arch. Surg. **72**:20, 1956.
40. Johnson, C. A.: Surg. Gynec. & Obst. **93**:735, 1951.
41. Johnson, C. A.: Surg. Gynec. & Obst. **55**:731, 1932.
42. Lewis, T., and Pickering, G. W.: Heart **16**:33, 1931.
43. Allen, E. V., Barker, N. W., and Hines, E. A., Jr.: Peripheral Vascular Diseases, Philadelphia, 1946, W. B. Saunders Co.
44. White, J. C., and Smithwick, R. H.: The Autonomic Nervous System, New York, 1948, The Macmillan Co.
45. Burton, A. C.: Temperature of Skin: Measurement and Uses as an Index of Peripheral Blood Flow, *in* Potter, V. R., Editor: Methods in Medical Research, Chicago, 1948, Yearbook Publishers, Inc.
46. Green, H. D., Perkins, W., and Abernethy, J.: Circulation **1**:1277, 1950.
47. Felder, D., Russ, E., Montgomery, H., and Horwitz, O.: Clin. Sc. **13**:251, 1954.
48. Stewart, G. N.: Harvey Lectures **149**:86, 1912-13.
49. Harris, K. E., and Marvin, H. M.: Heart **14**:49, 1927-29.
50. Bazett, H. C., Love, L., Newton, M., Eisenberg, L., Day, R., and Forster, R., II: J. Appl. Physiol. **1**:3, 1948.
51. Mendlowitz, M.: Angiology **1**:247, 1950.
52. Eurman, G. H., and Mendlowitz, M.: J. Appl. Physiol. **5**:579, 1953.
53. Horeman, H. W.: Comparison of Methods for Measuring Peripheral Blood Flow, Thesis, Utrecht, 1958, University of Utrecht.
54. Mendlowitz, M.: Proc. Soc. Exper. Biol. & Med. **85**:111, 1954.
55. Hensel, H.: Ztschr. Kreislaufforsch. **41**:251, 1952.
56. Hensel, H., and Bender, F.: Pflüger's Arch. f. d. gesamte Physiologie **263**:603, 1956-57.
57. Aschoff, J.: Pflüger's Arch. f. d. gesamte Physiologie **247**:31, 1943-44.
58. Barany, F. R.: Abnormal Vascular Reactions in Diabetes Mellitus, Lund, 1955, Hakan Ohlsson.
59. Wever, R., and Achoff, J.: Pflüger's Arch. f. d. gesamte Physiologie **264**:272, 1957.
60. Thron, H. L.: Pflüger's Arch. f. d. gesamte Physiologie **263**:127, 1956-57.
61. Mendlowitz, M., and Feitelberg, S.: J. Appl. Physiol. **8**:671, 1956.
62. Mendlowitz, M.: Science **107**:97, 1948.
63. Allen, E. V.: Proc. Staff Meet. Mayo Clin. **12**:187, 1937.
64. Laubry, C., and Meyer, J.: Arch. mal. coeur **15**:265, 1922.
65. Duryee, A. W., and Wright, I. S.: Am. J. M. Sc. **185**:664, 1933.
66. Wright, I. S., and Duryee, A. W.: Arch. Int. Med. **52**:545, 1933.
67. Roth, G. M.: Nailfold Capillaries in Man.[43]
68. Redish, W., and Rösler, H.: Wien. Arch. inn. Med. **16**:463, 1929.
69. Sucquet: Cited by H. W. Popoff.[73]
70. Hoyer, H.: Arch. f. microsk. Anat. **13**:603, 1877.
71. Grant, R. T., and Bland, E. F.: Heart **15**:385, 1929-31.
72. Grant, R. T., and Pearson, R. S. B.: Clin. Sc. **3**:119, 1938.
73. Popoff, H. W.: Arch. Path. **18**:295, 1934.
74. Masson, P., and Géry, L.: Ann. d'anat. path. **4**:153, 1927.

75. Burch, G. E., and Phillips, J. H., Jr.: Circulation Res. **6**:416, 1958.
76. Adams-Ray, J., and Nordenstam, H.: Ztschr. Zellforsch. **45**:435, 1957.
77. Lovell, R. R.: Clin. Sc. **9**:249, 1950.
78. Whittaker, S. R. F., and Winton, F. R.: J. Physiol. **78**:339, 1933.
79. Pappenheimer, J. R., and Maes, J. P.: Am. J. Physiol. **137**:187, 1942.
80. Green, H. D., Lewis, R. H., Nickerson, N. D., and Heller, A. L.: Am. J. Physiol. **141**:518, 1944.
81. Nichol, J., Girling, F., Jerrard, W., Claxton, E. B., and Burton, A. C.: Am. J. Physiol. **164**:330, 1951.
82. Mendlowitz, M.: J. Clin. Invest. **27**:565, 1948.
83. Yamada, S.: J. Appl. Physiol. **6**:495, 1954.
84. Yamada, S., and Burton, A. C.: J. Appl. Physiol. **6**:501, 1954.
85. Mendlowitz, M., Torosdag, S. M., and Sharney, L.: J. Appl. Physiol. **10**:436, 1957.
86. Gaskell, P., and Krisman, A. M.: Circulation Res. **6**:461, 1958.
87. Mendlowitz, M.: Circulation **3**:694, 1951.
88. Wilson, G. M.: Quart. J. Med., New Series **21**:201, 1952.
89. Mendlowitz, M., Grossman, E. B., and Alpert, S.: Am. J. Med. **15**:316, 1953.
90. Megibow, R. S., Pollack, H., Megibow, S. J., Bookman, J. J., and Osserman, K.: Am. J. Med. **15**:322, 1953.
91. Mendlowitz, M., and Naftchi, N.: (Abstract) Circulation **16**:915, 1956; J. Appl. Physiol. **13**:247, 1958.
92. Mendlowitz, M., Gitlow, S., and Naftchi, N.: (Abstract) Fed. Proc. **17**:110, 1958; J. Appl. Physiol. **13**:252, 1958.
93. Mendlowitz, M., and Touroff, A. S. W.: Circulation **5**:577, 1952.
94. Goetz, R. H.: South African M. J. **21**:2, 1947.
95. Edwards, E. A.: New England J. Med. **250**:709, 1954.
96. Ratschow, M.: Third World Congress of Cardiology, Brussels, Abstract, Round Table Conference, 1958, p. 251.
97. Mendlowitz, M., and Naftchi, N.: Unpublished data.
98. Abramson, D. I.: Vascular Responses in the Extremities of Man in Health and Disease, Chicago, 1944, Univ. of Chicago Press.
99. Winsor, T., Payne, J. H., Rudy, N., and Beatty, J. O.: A.M.A. Arch. Surg. **74**:21, 1957.
100. Mendlowitz, M., Parets, A. D., Gold, T., and Drachman, S. R.: J. Chron. Dis. **7**:484, 1958.
101. Mendlowitz, M., Parets, A. D., Gold, T., and Drachman, S. R.: J. Chron. Dis. **7**:493, 1958.
102. Mendlowitz, M., Altchek, A., and Naftchi, N.: Am. J. Obst. & Gynec. **76**:473, 1958.
103. Winsor, T.: Am. J. M. Sc. **224**:42, 1952.
104. Goetz, R. H.: Angiology **2**:1, 1951.

Book Review

THE AUTHOR-PUBLISHER-PRINTER COMPLEX. By Robert S. Gill, Ed. 3, Baltimore, 1958, Williams & Wilkins Company, 134 pages. Price $2.25.

As observed by the author, "much grist has come to the mill" since publication of the first and second editions of *The Author-Publisher-Printer Complex*. The "mill" of printing and publishing is a complex structure, and although, as with other modern businesses, changes are continually taking place, the basic concepts of this ancient art remain fundamentally the same.

This is a book which definitely should be read and digested by all members of the fourth estate. While it is largely devoted to providing guidance to those engaged in printing and publishing scientific works, the book has a place in the libraries of authors, publishers, and printers. In fact, it should also be read by all who are in any way connected with "printer's ink."

The transmutation of an original manuscript into print appears to the uninitiated as a simple task. Author Gill has done his best to preserve this premise, whereas, in actual fact, the job is a complex one requiring the undivided attention of professional men and women skilled in their own particular related spheres of the craft. The word related is used because the various steps from the time the author sets pen to paper until a book is delivered in complete form bear a definite relation one to the other.

The business of writing, publishing, and printing has many facets. The principals involved in the publication of a book—the author, publisher, and printer—are inextricably linked together throughout the whole process from start to finish. It is essential, therefore, that each one knows his job and is worthy of his hire, because a weak link in the chain can cause costs to skyrocket out of all proportions.

Mr. Gill explains in a simple, practical way the duties of the principals involved in producing a scientific book. He obviously has considerable knowledge of the art of printing and publishing and of the printing process He deals with illustrations, the reading of proof and proof reading, revision, literary property and inheritance, royalties, etc.

His explanations and descriptions conform to a definite pattern. This is, perhaps, a trifle naive because if everything in the printing and publishing of authored works went according to schedule and followed the rules of traditional conformity, it would be little short of miraculous!

There are so many factors which can upset any prescribed and well-defined pattern. For example, the author can disrupt the basic cost structure by inserting an overdose of author's alterations; the publisher can do a mediocre job of promotion, and the printer—that indefinable craftsman as temperamental as a virtuoso of the pianoforte—has it within his power to sadden the author's life or make glad his heart and, at the same time, provide the publisher with a brand new ulcer!

However, Mr. Gill's latest edition is commended to those who toil with words and those who produce them for the general edification of the reading public.

J. M. M.

Announcements

THE AMERICAN SOCIETY FOR ARTIFICIAL INTERNAL ORGANS will meet at The Shelburne Hotel in Atlantic City, New Jersey, on April 12 and 13, 1959.

A Symposium on THE HEART: ELECTROCARDIOGRAPHY will be presented on Feb. 23 and 24, 1959, at the University of Kansas School of Medicine. Dr. Enrique Cabrera, National Institute of Cardiology, Mexico City, Dr. Herman K. Hellerstein, Western Reserve University, and Dr. J. Willis Hurst, Emory University, will participate in the informal sessions of this course. They will compare and correlate their interpretations of a group of unknown clinical electrocardiograms, which have been carefully selected to pinpoint problems encountered daily in the practice of medicine. For program announcement and other information, write: Department of Postgraduate Medical Education, University of Kansas Medical Center, Kansas City 12, Kans.